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ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL CANCER INSTITUTE
FISCAL YEAR 1979
PART V

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service   National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

U.S. NATIONAL CANCER INSTITUTE

Fiscal Year 1979

Part V

Division of Cancer Research Resources and Centers

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NATIONAL CANCER INSTITUTE

DIVISION OF CANCER RESEARCH RESOURCES AND CENTERS

ANNUAL REPORT

October 1, 1978 through September 30, 1979

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FOREWORD BY THE DIRECTOR

By the beginning of the fiscal year 1979, as a result of reorganizing the National Cancer Institute (NCI), all of the regular research grant programs had been transferred from the Division of Cancer Research Resources and Centers (DCRRC) to other Divisions of the Institute. Responsibility for all peer review of grants and research contracts had been transferred from other Divisions of the Institute to DCRRC. In addition, DCRRC had accepted responsibility for activities related to supporting and interacting with the National Cancer Advisory Board (NCAB). The Division continued to administer grants management and grants financial management, as well as reporting and analysis activities. The Division also continued the administration of the Organ Site Programs, the Construction Program, and Clinical and Research Manpower Programs. The continuance of the latter programs in DCRRC was a temporary arrangement to provide stability while other transfers were being assimilated and to provide time to consider the proper organizational setting for them.

In April 1979, the Director of NCI announced tentative plans to initiate a second phase of the Institute's reorganization. This second phase of reorganization would remove the Centers Program from the Office of the Director, NCI; would remove Organ Site, Manpower, and Construction Programs from DCRRC; and would combine these Programs with major elements of Cancer Control in a new Division. The Director also indicated tentative plans to create a Division of Prevention.

As fiscal year 1979 draws to a close, plans to implement this second phase of reorganization are being formulated. Since the anticipated changes have not been accomplished, this annual report includes the programs that soon will be transferred from the Division. Furthermore, until a name change is authorized, the report continues under the appellation Division of Cancer Research Resources and Centers,

The Division takes pride in the activities, the progress, and the accomplishments of the Research Analysis and Evaluation Branch, the National Organ Site Programs Branch, the Research Facilities Branch, the Clinical Cancer Education Branch, and the Research Manpower Branch. Because these activities are sufficiently described in individual Branch reports, no further comment is needed here. Incorporating new review responsibilities into the activities of the Review and Referral Branch and coping with the additional complications and logistical difficulties imposed on the Grants Administration Branch by the reorganization of the Institute commanded much of the energy and effort of the Division during the fiscal year. These time- and resource-consuming endeavors are well documented in the reports of these two branches.

An emerging role for the Divisions is the provision of grants financial, procedural, and policy information and advice to the Institute's Division Directors and to the Director, NCI. This role is a natural consequence of the information and data that become available to DCRRC through the receipt, referral, review, and award processes. The importance of this service resulted during fiscal year 1979 in the creation of the Grants Financial and

Data Analysis Branch, formerly the Grants Financial Section of the Grants Administration Branch. It is also bringing about increased awareness and consolidation of the Division's functions in formulating general NCI policy and procedures such as announcement of new initiatives through Program Announcements and Requests for Applications (RFA's).

The most important new activity of the Division is its relation to the National Cancer Advisory Board (NCAB). As a result of the Institute's reorganization, the Director of DCRRC became the Executive Secretary of the Board. The Division also retained the Executive Secretariate of the NCAB Subcommittee on Special Actions. Consequently, DCRRC not only continued its responsibility for preparing for the Board's review of grants, but also became the focal point for interacting with the Board and senior Institute staff on matters related to Board agendas, coordinating NCAB subcommittees, nominations to the Board, and the conduct of Board meetings.

An important development this fiscal year was the creation of a Board subcommittee to assess Board activities and to develop measures to maximize the Board's fulfillment of its responsibilities. The Director, DCRRC, serves as Executive Secretary of this subcommittee. The creation of this subcommittee is propitious because it came at a time when a new chairman, new appointments, and new legislation made considerable changes in the composition of the Board. The 1979 amendments to the National Cancer Act added six ex officio members to the Board, specified that at least five members be knowledgeable in environmental carcinogenesis, and required that two members of the Board be physicians who care for cancer patients. The Board now consists of eighteen voting members appointed by the President and eleven nonvoting ex officio members.

OFFICE OF THE SPECIAL ASSISTANT FOR SPECIAL PROJECTS

A variety of coordinating activities were performed in the Office of the Special Assistant for Special Projects. The principal activities were concerned with the following: (a) Freedom of Information (FOI) and Privacy Act (PA); (b) National Cancer Advisory Board; (c) DNA recombinant research; (d) Cancer Research Emphasis Grants (CREG), and later, Request for Applications (RFA); and (e) conference support, both by R-13 grants and Fogarty International Center (FIC) contracts. Each of these activities will be addressed in turn.

Freedom of Information and Privacy Act

This office serves as a coordinating point and in an advisory capacity for FOI and PA requests pertaining to NCI grants. Privacy Act requests pertaining to a single program are routinely routed through this office to a Program Director; and the office coordinates, advises, and collates the response to the more complicated Freedom of Information requests.

The following table reflects the volume of requests answered.

PUBLIC INFORMATION REQUESTS

Calendar Year 1978 *	
PRIVACY ACT REQUESTS:	1, 789
FREEDOM OF INFORMATION ACT REQUESTS:	35
Calendar Year 1979 *	
PRIVACY ACT REQUESTS:	1,672 **
FREEDOM OF INFORMATION ACT REQUESTS:	24 **

* NIH reports Freedom of Information Act and Privacy Act requests by calendar year, not fiscal year.

** Estimated, based on actual number for January 1, 1979 through March 30, 1979.

National Cancer Advisory Board

Activities concerned with the NCAB include not only the routine planning of pre and post-Board meetings, but more importantly, advising staff of all Divisions regarding policy and procedures and serving as Executive Secretary of the Special Actions Subcommittee. An interesting activity of the Subcommittee this year was the examination of two basic science grant programs— Viral Oncology and Immunology.

DNA Recombinant Research

The Special Assistant serves as a member of the Executive DNA Committee and, in addition, is responsible for assuring that all NCI grants of which DNA recombinant research is a part, are cleared by the NIH Office of Recombinant DNA Activities.

A summary of activities in fiscal year 1979 is as follows:

RECOMBINANT DNA PROJECTS

PROGRAM AREA	NUMBER OF PROJECTS	DIRECT COSTS *
MULTIDISCIPLINARY	10	$ 9,062,390
VIRAL ONCOLOGY	31	6,872,993
TUMOR BIOLOGY	32	5,016,820
RESEARCH TRAINING	28	2,179,017
RADIATION	2	1,454,209
IMMUNOLOGY	5	1,245,300
DRUG DEVELOPMENT	2	451,449
CARCINOGENESIS	5	349,070
CREG - CP	2	159,245
	117	$ 26,790,493

* This does not represent the amount spent on DNA recombinant research; it is the total amount for a grant in which DNA research may be a major or minor fraction.

Cancer Research Emphasis Grants

The CREG Program saw little increase in activity this year. The CREG program as such is now being phased down to be supplanted by a program in which RFA's (Request for Applications) are used if applications for a definite project are desired; or a program announcement if applications in a broader area of research are requested. Present levels of CREG/RFA support are as follows:

CREG PROGRAM

(FY-79 - Includes Grants Awarded and those to be Awarded)

DIVISION	RFA #	# GRANTS	RECOMMENDED OR AWARDED DIRECT COSTS	TOTAL COSTS
DCBD	NONE	NONE	NONE	NONE
DCT	01	2	$ 113,504	$ 147,436
	03	8	1,002,057	1,325,161
	04	11	981,120	1,574,240
	05	4	282,208	384,567
	06	3	234,381	341,928
DCCP	01	4	226,702	301,199
	02	4	359,612	496,057
	03	4	226,450	332,081
	04	1	61,107	73,830
	10	1	99,492	118,787
	14	2	108,797	131,697
	15	2	159,436	245,714
	16	2	212,729	299,300
	17	7	288,766	404,270
	18	5	269,702	379,539
	19	4	173,769	232,023
	20	2	130,933	177,561
	22	1	127,529	178,540
	29	2	26,632	29,765
	30	2	102,714	173,978
	31	1	8,125	14,802
	32	1	50,000	50,000
	33	2	231,834	305,144
TOTAL	20	75	$ 5,477,599	$ 7,717,619

Conference Support

The bulk of extramural conference support is through R-13 grants or Fogarty International Center contracts. In general, an R-13 grant is appropriate if the subject of the conference is of prime relevance to one Institute; the FIC contract if the subject is of interest to several B/I/D's.

The following tables summarize NCI's support of conferences:

FOGARTY CONFERENCES - FY '78

PROGRAM	DIRECT COST	NUMBER
Viral Oncology	$ 19,500	4
Carcinogenesis	4,500	1
Clinical	18,000	2
Tumor Biology	58,500	9
Drug Development	15,000	1
Immunolgy	56,000	7
Radiation	7,000	1
	$ 178,500	25

FOGARTY CONFERENCES - FY 79 *

PROGRAM	DIRECT COST	NUMBER
Viral Oncology	$ 40,000	3
Carcinogenesis	-	0
Clinical	-	0
Tumor Biology	72,919	13
Immunology	40,000	6
Epidemiology	4,000	1
Multidisciplinary	15,000	1
	$ 171,919	24

*Figure based on approximately nine-month period from October '78 to June '79.

Table 1

R-13 Grants - FY 79 *

Total No. Paid:		12
Total Cost:		$ 506,322
Priority Score:	Mean	165.5
	Median	181
Average Cost:		$ 42,193

Table 2

R-13 FY - 79 by Cancer Activity *

	Number	Total
Tumor Biology	2	$ 136,930
Immunology	-	
Epidemiology	1	$ 93,123
Breast Cancer	1	3,308
Carcinogenesis	1	$ 26,378
Viral Oncology	2	$ 125,240
Clinical	2	$ 45,784
Radiation	2	61,350
Drug Development	1	14,209
Total	12	$ 506,322

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* These figures are based on approximately 9-month period from October '78 to June '79.

NATIONAL ORGAN SITE PROGRAMS BRANCH

The National Organ Site Programs consist of grant-supported National Projects of targeted cancer research. Each Project is a planned research effort oriented toward cancer at a specific organ site. Currently there are National Organ Site Projects concerned with cancers of the urinary bladder, large bowel, pancreas, and prostate. The planning, direction, and coordination of each Project are provided at a headquarters institution other than the NCI. A national project director, who is not an employee of NCI, is assisted in planning and administration by a Headquarters staff and by a working cadre of active research scientists recruited from institutions throughout the Nation. Grant applications are received by the headquarters and are reviewed by the working cadre and by the National Cancer Advisory Board. Applications which are judged scientifically meritorious and relevant to the aims of the Project are recommended to the NCI for funding.

Each national project director is a recognized clinical or laboratory scientist with a strong interest in, and professional identification with, a specific organ site cancer. The National Bladder Cancer Project is under the direction of Dr. Gilbert H. Friedell, St. Vincent Hospital, Worcester, Massachusetts; the National Large Bowel Cancer Project, Dr. Murray M. Copeland, M. D. Anderson Hospital and Tumor Institute, Houston, Texas; the National Pancreatic Cancer Project, Dr. Isidore Cohn, Jr., Louisiana State University School of Medicine, New Orleans, Louisiana; and the National Prostatic Cancer Project, Dr. Gerald P. Murphy, Roswell Park Memorial Institute, Buffalo, New York.

NATIONAL BLADDER CANCER PROJECT

Description

The primary goal of the National Bladder Cancer Project is to sponsor and encourage laboratory and clinical research directed toward improving the techniques available for managing, controlling, or preventing cancer of the urinary bladder.

A multidisciplinary research program has been developed to encourage collaboration and exchange of information between clinical and laboratory scientists engaged in studies related to bladder cancer. Studies are supported which seek (1) to identify carcinogenic factors and develop methods for minimizing their effect, (2) to improve detection methods and identify new high-risk populations, (3) to increase understanding of the pathogenesis and carcinogenesis processes and find methods for interferring with these processes, (4) to develop improved methods of diagnoses in order to identify those patients most suitable for a specific available treatment regimen, and (5) to find better methods of treating the disease.

Two collaborative efforts are being supported by the NBCP for prospective studies of patients with bladder carcinoma: The National Bladder Cancer Project Confederation and National Bladder Cancer Collaborative Group A. The Confederation conducts Phase II studies searching for new, more effective compounds. It currently consists of three institutions: Mayo Clinic, Memorial Sloan-Kettering Cancer Center, and Wayne State University School of Medicine. Collaborative Group A is continuing follow-up studies of patients who were entered into one or more of four protocols--a surveillance of all patients with bladder cancer admitted to the participating institutions; a study of multiple mucosal biopsies from patients with frank tumor or positive cytology; an evaluation of intravesical therapy with thio-TEPA; and a study comparing radiation therapy alone to radiation therapy plus cystectomy for invasive carcinoma. The group has initiated three new protocols--a Phase III study of systemic chemotherapy in patients with bladder carcinoma; a Phase III study of systemic chemotherapy as adjuvant to definitive radiation and surgical therapy of invasive bladder carcinoma; and a Phase I/II study of chemoprevention of recurrence in patients with completely resected low-stage lesions. Collaborative Group A consists of twelve institutions: Massachusetts General Hospital, University of Tennessee, Virginia Mason Research Center, Rush Presbyterian-St. Luke's Medical Center, St. Vincent Hospital, University of Oregon, Medical College of Virginia, Roswell Park Memorial Institute, University of Iowa, University of California at San Diego, Johns Hopkins Hospital, and Georgetown University.

In addition to these collaborative efforts, over thirty independent studies related to bladder cancer are currently supported through the Project. These studies vary in size and include both laboratory and clinical investigations. Investigators from various disciplines are engaged in research in the categories of epidemiology and etiology, experimental biology, detection and diagnosis, and therapy.

Accomplishments

The ability to study the constituents of urine from humans and the availability of unique animal models have led in the past year to much new information on the pathogenic and carcinogenic processes leading to bladder cancer. Every indication suggests that the rate at which knowledge is accumulating will continue over the next few years and that the information obtained about this disease will contribute to an improved understanding of the more general process of carcinogenesis. The ability in studies of the bladder to separate the metabolism of carcinogenic factors from that carried out by the liver and to exploit the relatively low normal metabolic activity and mitotic rate of the urothelium have assisted in the delineation of steps in the process of carcinogenesis.

Much has been learned from the study of suspected compounds or their metabolites in the urine. Dimethylnitrosamine (DMN) has been detected in the urine of individuals with infectious cystitis associated with the presence of nitrite, and DMN formation has been identified in the urine from nitrite and various pharmacological agents (Radomski *et al*. 1978). More recently, using very sensitive techniques, it has been possible to detect that microsomes from the urinary bladder of dogs are able to metabolize DMN to its active carcinogenic form (Radomski *et al*.1979). It is suggested that the formation of DMN may play a role in the etiology of human bladder cancer. In other studies, it was concluded that in the acidic conditions of the urine the noncarcinogen 1-naphthylamine is not released as the N-hydroxy-N-glucuronide, as is its carcinogenic isomer 2-naphthylamine (2-NA), but is further metabolized by an acid catalyzed bimolecular rearrangement to 1-amino-4-naphthol-N-glucuronide from the N-hydroxy conjugate. This reaction, which is limited to aromatic amine derivatives with an unsubstituted para position, diverts the otherwise active N-hydroxy metabolites to inactive products and, therefore, may account for the failure of the 1-NA to cause bladder cancer (Hearn *et al*. 1979).

The integration of *in vivo* and *in vitro* data is essential in order to understand the mechanism of carcinognensis. An example of such a combined study has recently been reported (Brill *et al*. 1979). Since the carcinogenicity of the arylamines for the dog bladder mucosa appears to require their metabolic conversion to unconjugated N-oxidized derivatives, the N-oxidation of 2-fluorenylamine and 3-dibenzofuronylamine was investigated *in vitro* employing fortified dog liver microsomes. The identification and quantitation of the N-oxidized metabolites were performed employing gas chromatography. It could be shown that pretreatment of the dogs with phenobarbitol before isolation of the microsomes stimulated the N-oxidation of both amines three-to seven-fold. Since this range of N-oxidation falls within the range of arylamines known to be carcinogenic, it suggests that these arylamines are bladder carcinogens and that phenobarbitol would enhance their carcinogenicity. *In vivo* studies in dogs are now in progress to test this hypothesis.

Evidence is now available that there are probably at least two stages in bladder carcinogenesis. In studies where male Fischer rats were fed 0.2 percent N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) in the diet, it was shown that animals fed FANFT for six weeks followed by control diet had few tumors. However, if sodium saccharin 5 percent or DL-tryptophan 0.2 percent were fed immediately after or six weeks after FANFT administration, a high incidence of bladder cancer was obtained. Saccharin was found to be a much more potent promoting agent than tryptophan. The control diet, saccharin, or tryptophan fed alone gave no tumors. In the same study, pleomorphic microvilli were observed by scanning electron microscopy on the surface of all tumors examined and on the surface cells of hyperplastic bladder epithelium after six weeks of FANFT followed by six weeks of saccharin, but not after six weeks of tryptophan feeding (Cohen *et al*. 1979; Cohen *et al*. 1978). A growth-stimulating effect of normal urine on normal or FANFT pretreated rat bladder epithelium was demonstrated in experiments utilizing heterotopic bladders (Oyasu *et al*. 1979) transplanted into the gluteal muscle of male Fischer rats or in animals with urinary diversion. Some of the animals pretreated with 0.2 percent FANFT in the diet for 14 weeks developed tumors of the bladder if the urine was not diverted. In animals similarly pretreated with FANFT, no bladder tumors were seen when the urine was diverted by uterosigmoidostomy (Oyasu *et al*. 1979). These studies provide support for an initiation and promotion phase of bladder carcinogenesis.

It is to be hoped that in the future, many of these facets of carcinogenesis now only possible *in vivo* will be conducted *in vitro*. Recently two very promising techniques have been described which allow cells of the urothelium to grow as organized stratified layers of epithelial cells (Chlapowski *et al.* 1978; Leighton *et al*. 1979).

Many new efforts have been made to find cellular and tissue markers which have prognostic significance. 1. A study between desmosomal ultrastructure and tissue invasiveness indicates that desmosomes are abundant in invading nests of tumor cells. Such a finding probably reputes the idea that decreased intercellular adhesion is a prerequisite for invasion, since strong interadhesion of cells is probably a function of the area occupied by the intercellular junctions (Pauli *et al.* 1978). Recent studies indicate that FANFT induces an increase in intramembrane particle numerical densities which parallels the transformations observed in the early stages of malignancy in human bladder epithelium. This suggests that the FANFT model is well suited for studies on the relationship of membrane structure and tumor biological behavior (Pauli *et al.* 1978). 2. A recent study indicates that pleomorphic microvilli of the cell membrane as observed by scanning electron microscopy, which were first described in tumors of the FANFT model, may be useful in following people at high risk for developing bladder cancer, such as those being followed for recurrence or those industrially exposed to carcinogens (Jacobs *et al.* 1979). 3. Blood group isoantigens A and H (O) were measured in radical cystectomy specimens. Isoantigens were absent in areas showing either atypia or carcinoma *in situ*. Blood groups isoantigens were absent in approximately half of the sections of histologically normal epithelium. It is suggested that these areas of epithelium which appear benign according to the conventional histological criteria, but in which the blood group isoantigens are absent, may represent areas of low grade carcinomas *in situ* (Weinstein *et al.* 1979). 4. The increase of galactosyl transferase seen in the bladder tumors and in the urine and bladder washings of tumor-bearing patients was found to be independent of tumor stage and grade, but offers a promising basis for the detection of bladder tumors (Hagen-Cook *et al.* 1978).

Changes in the immunologic parameters of the host with prognostic significance have been found. The decrease in responsiveness of patients with transitional cell carcinoma of the bladder to challenge with dinitrochlorobenzene (DNCB) has been observed to correlate well with advancing stages of the disease (Bean *et al.* 1978; Brosman *et al.* 1979). Lymphocyte response in mixed lymphocyte culture and to concanvaline A (Con A) blastogenesis was found to be decreased in bladder cancer. A further decrease to Con A occurred as the disease advanced in stage (Bean *et al.* 1978; Cummings *et al.* 1978). In an effort to match the patient with the most appropriate available treatment, the use of cytology and selected site biopsy is being expanded to identify those individuals who have *in situ* lesions not visible by cystoscopy (Heney *et al.* 1978; Loening *et al.* 1978).

Emphases and Projections

Efforts will continue to be made to improve the chemotherapy of bladder cancer and to initiate treatment earlier in the course of the disease. The NBCP Confederation is evaluating the effectiveness of new drugs through Phase II studies in an attempt to find more effective agents for this disease. The National Bladder Cancer Collaborative Group A, in a Phase III study will evaluate the effectiveness of *cis*-diamminedichloroplatinum (*cis*-Platinum) as an adjuvant to definitive radiation plus surgical therapy. It will continue its study comparing *cis*-Platinum and *cis*-Platinum plus Cytoxan for definitive chemotherapy for metastatic disease, and its study using 13-*cis*-retinoic acid in an attempt to prevent the recurrence of superficial disease. *Cis*-Platinum appears to be the most effective agent against bladder cancer yet developed. In tests of the FANFT mouse model, a striking additive effect has been found between radiation therapy and *cis*-Platinum therapy. Initial studies in animals suggest that *cis*-Platinum may be effective intravesically to treat the flat *in situ* lesions of the bladder.

The conditions influencing recurrences and the enhancement or inhibition of the growth of bladder tumors are actively being studied: the potential implantation of tumor cells on denuded surfaces of the bladder wall after surgery, the possible cytotoxic effect of cytoscopic fluids on the bladder epithelium, and the factors which modify the immunological system of the host. Initial findings in other studies regarding such endogenous compounds as prostaglandins and interferon suggest that they may play a role in the success or failure of present treatment.

Efforts have been continued to improve the diagnosis of bladder cancer in order to permit the most appropriate treatment selection. The new hybridoma technique in which clones of hyperimmune spleen cells fused with myeloma cells are isolated *in vitro*, provides a mechanism for the isolation and multiplication of a cell which makes a single specific antibody. This technique is being utilized in an attempt to develop an assay for tumor-associated antigens in the plasma and urine.

The new information on the initiation and promotion of bladder cancer has stimulated an interest in attempts to inhibit this process. Evidence from animal studies that promotion can be modified raises the possibility that tumors can be inhibited at a more advanced stage of tumor development than was formerly believed.

Analysis of the data obtained from an international epidemiology study of the factors related to the etiology of bladder cancer has been initiated. Although the principal aim of this study is to evaluate the possible role of coffee in bladder cancer, information on other factors such as cigarette smoking, occupation, and artificial sweeteners will be obtained. Additional relevant information will be obtained as a spin-off on the national study of artificial sweeteners being managed through NCI.

Other Program Activities

In order to promote communication among investigators with common interests and to further the exchange of information between laboratory and clinical scientists, an Investigators' Workshop was held in Sarasota, Florida, on December 13-15, 1978. This meeting was open to anyone interested in bladder cancer research and/or clinical management.

The initial session reviewed the status of the therapy for bladder cancer with emphasis on the advances in chemotherapy. Poster sessions were held to provide information on ongoing studies supported through the Project. Major addresses were given on the subjects of chemical carcinogenesis, chemoprevention, the role of statistics in research, and the search for markers of bladder carcinogenesis. Evening sessions were held to discuss the following research areas as they relate to cancer of the bladder: cell-mediated immunity; chemical intervention; initiation and promotion stages of carcinogenesis; the recognition of cells; and the utilization of a computer model to evaluate the feasibilty of screening.

A U.S.-Japan Cooperative Research meeting was held in Sarasota on December 10-13, 1978, immediately preceding the Investigators' Workshop. Nineteen clinical investigators from the U.S., all active in the NBCP, met with twelve leaders of clinical research on bladder cancer from Japan. The current status of studies on the epidemiology, diagnosis, and therapy of bladder cancer being conducted in the two countries was discussed and information was exchanged as to the best new approaches which could be exploited. The U.S. participants then reviewed the requirements and benefits of cooperative clinical studies in bladder cancer as they are being conducted in the United States. Since all participants in the U.S.-Japan meeting remained in Sarasota to attend the Investigators' Workshop, exchange of information continued throughout the week.

A review of the progress of laboratory and clinical research in bladder cancer appears in the June issue of Seminars in Oncology, 1979. This issue, edited by the National Bladder Cancer Project staff, has four major divisions entitled: Understanding the Disease; Assessing the Disease and Host; Therapeutic Approaches Based on Disease Assessment; and Research Probes and Planning Techniques. This critical evaluation of the field assists in meeting several objectives of the Project, to transmit to the practicing physician the latest advances in the management of bladder cancer and to define for laboratory investigators clinical problems which require further study.

To further assist in the transmission of current information to the practicing physician, the NBCP, in cooperation with the American Cancer Society, assisted in the development of a half-day session on cancer of the bladder and made available pertinent information to participants of the American Cancer Society National Conference on Urologic Cancer which was held in Los Angeles, California on April 4-6, 1979.

NATIONAL BLADDER CANCER PROJECT
(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
34	$3,030	18	$2,009	52	$5,039

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NATIONAL LARGE BOWEL CANCER PROJECT

Description

The National Large Bowel Cancer Project, with headquarters at The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, sponsors multidisciplinary basic and clinical programs of research designed to examine the biology and promote the control of colon and rectal cancer. These objectives are pursued by encouraging research grants in a spectrum of programs designed to: 1) identify the causes of large bowel cancer and their inhibitors, 2) identify and clarify biochemical and molecular controls, 3) identify individuals at high risk, 4) promote early diagnosis and prevention of large bowel cancer, 5) apply modern pharmacologic methods in the development of new chemotherapeutic treatments, 6) apply modern tumor immunobiology in the development of diagnostic markers, methods of treatment, and prevention of large bowel cancer, 7) develop clinical research treatment programs, and 8) promote interdisciplinary communications and collaborative research programs among grantees of the National Large Bowel Cancer Project.

Knowledge derived from these areas of investigation will have applicability in the design of sound research programs to improve management and treatment and thereby provide the basis for the control of this disease.

Accomplishments

Identification of Large Bowel Cancer Causes and Their Inhibitors

Research on the metabolism and inhibition of several colon carcinogens in animal models has been pursued. It has been determined that the organospecificity exhibited by the colon carcinogen methylazoxymethanol (MAM) is due to its metabolism by NAD^+/$NADP^+$-dependent dehydrogenases in organs sensitive to its acute and chronic effects (Zedeck, 1978). Pyrazole, an inhibitor of alcohol dehydrogenase, inhibits the acute effects of this carcinogen while disulfiram, an inhibitor of aldehyde dehydrogenase, potentiates its effects (Fiala et al, 1978; Zedeck and Tan, 1978). Treatment of animals with pyrazole prior to their receiving MAM results in incomplete inhibition of tumor development in the intestine (Zedeck and Tan, 1978), suggesting that pathways other than alcohol dehydrogenase may be active. The nature of the resistance of the Lobund Wistar rat to dimethylhydrazine (DMH)- induced colon cancer was found to be partly due to metabolic activation of DMH and to other as yet undetermined endogenous factors (Pollard and Zedeck, 1978).

An important contribution has been the demonstration that the colon mucosa contains a competent drug metabolism system capable of hydroxylating a wide variety of compounds (Fang and Strobel, 1978a). The hydroxylation of certain drugs and carcinogens by colonmicrosomes is stimulated by pretreatment with the gastrointestinal hormone gastrin. It has also been shown that colonic cells are capable of activating carcinogens to mutagenic metabolites (Fang and Strobel, 1978b).

Studies on the metabolic epidemiology of colon cancer have been conducted. Although no relationship is apparent in fecal profiles of the anaerobic microflora of patients with large bowel cancer or with nonhereditary large bowel polyps compared to control subjects, the activities of fecal microbial $^7\alpha$-dehydroxylase and cholesterol dehydrogenase are significantly elevated in these patients compared to controls (Mastromarino et al, 1978).

Techniques have been established for preparing nuclear and cytoplasmic RNA populations free of cross-contamination. RNA has been prepared from these fractions and from total colonic mucosal cells. These techniques will allow investigation of changes in processing of nuclear RNA which may occur during induction of colon cancer in mice by DMH (Augenlicht, 1978).

Kim has demonstrated that rats fed a fiber diet (crystalline cellulose) have a 50 percent reduction in the incidence of DMH-induced colon tumors compared to rats fed a fiber-free diet. The effects appear to be related to the duration of fiber ingestion and to the differential fiber effect on either the luminal content or the mucosa of proximal and distal colon (Freeman et al, 1978). The findings support the hypothesis that fiber is a protective agent against the development of colonic neoplasms.

Identification and Clarification of Biochemical and Molecular Controls of Large Bowel Cancer

The production of a melanocyte contact inhibitory factor (MCIF) has been maintained and used to study the effects of this growth regulatory macromolecule upon a broad spectrum of human colon carcinomas maintained *in vitro*. The sources, specificity, biochemical characterization, and mechanisms of action of MCIF have been studied and progress has been made in purifying the contact inhibitory activity. (Lipkin et al, 1978).

A differentiation-induction model utilizing N,N-dimethylformamide(DMF)-treated human colon carcinoma cell lines has been established. DMF reversibly induced a less malignant phenotype with concomitant maturational effects in cultured human colon carcinoma cells (Dexter et al, 1979), opening areas of interest with regard to the relationship between the rate of cell proliferation and the appearance of a differentiated phenotype. The results suggest that an established tumor line may irrevocably lose the controls needed to maintain the differentiated state in the absence of a growth suppressant.

Changes in cell surface glycoconjugates in malignancy and during normal differentiation have been reported (Siddiqui et al, 1978; Tsao and Kim, 1978; Murty et al, 1978). The effects of sodium butyrate and dimethylsulfoxide on cultured colon cancer cell lines (SW480 and SW 460) *in vitro* and on surface glyco-conjugates have been examined (Freeman and Kim, 1978). The effects of butyrate on changes in chromatin structure have also been studied (Vidali et al, 1978 a and b). Butyrate-treated cells respond by increasing the level of acetylation of histones, effectively changing the structure of nucleosomes to release constraints on the DNA strand. Increased accessibility of the DNA template is reflected in changing patterns of transcription. Removal of butyrate results in a rapid deacetylation of the histones and a decrease in DNA template capacity (Boffa et al, 1978). Likewise, the removal of the butyrate from the colonic tumor lines studied by Kim also leads to reversal of the changes and retardation of the more malignant phenotype (Freeman and Kim, 1978).

Another grantee has reported that chemical carcinogenesis changes the immunochemical specificity of colonic chromatin nonhistone protein complexes with DNA to that characteristic of colon adenocarcinoma. Antigenicity appeared in the DMH-treated rat colon in 4 weeks, long before pathological indications of malignancy were evident. Antibody specificity for colonic tumors has been established, and nuclear localization of the tumor-associated antigens was confirmed by immunohistochemical methods (Chiu et al, 1979; Markert et al, 1978).

N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and other nitroso or nitro compounds rapidly activate the guanylate cyclase (GC)-cyclic guanosine monophosphate system. The mechanism of MNNG activation of GC and factors modulating that action in epithelial cells appear to involve the formation of a paramagnetic complex with the characteristics of nitrosyl-heme (DeRubertis et al, 1978).

Early Diagnosis and Prevention of Large Bowel Cancer

Retinoic acid-binding proteins (RABP), although readily detectable in embryonic colon, are not evident in the colonic epithelium of adults and have been detected only in tumor lines with high metastatic potential. A number of human adenocarcinomas also contain RABP, but segments of normal human colon do not. Of particular interest is the observation that colonic epithelium in proximity to the tumor also showed the presence of the binding protein suggesting a possible reactivation of embryonic genes in the premalignant state. Measurement of RABP may have potential as diagnostic and prognostic probes in malignant colon tumors. The limits and sensitivity of detection of RABP in terms of cell numbers have been achieved using mouse colon tumor 26 as a model (Sani et al, 1979).

In the area of prevention, attention is being paid to screening and early detection. A controlled trial of screening for colorectal cancer utilizing fecal occult blood testing and sigmoidoscopy in standard risk patients (men and women age 40 and older) has been undertaken. During the past five years of the project, approximately 25,000 screening and rescreening examinations have been performed. Patient compliance has been high and the rate of positivity of the slides has been manageable with a high predictive value of preneoplastic lesions among positive screenees and low false-positivity and false-negativity for cancers. The staging of cancers at surgery in asymptomatic patients screened positive has been very favorable. The observations to date strongly suggest the need for 6 slides per patient during a 3-day testing period. Both laboratory and clinical observations suggest significant variability in the sensitivity of the methods and materials used.

The Hemoccult II slide with rehydration is the most sensitive. However, rehydration increases the sensitivity to the point where a significant increase in false positives is observed. Thus, this procedure is not recommended. The variations indicate the need for standardization of the techniques used (Winawer, 1978; Lipkin *et al*, 1978).

The sensitivity and specificity of diagnostic techniques were evaluated in 91 Hemoccult-positive patients with documented neoplastic lesions of the colon. (Winawer *et al*, 1978). The evaluation of tumor markers in lavage fluid has been largely unproductive. The only positive correlation that has been consistent, is surface labelling in patients with neoplastic lesions and in a small group of patients who were Hemoccult-positive and in whom no significant neoplastic lesion has been observed (Deschner *et al*, 1978).

Identification of Individuals at High Risk for Development of Large Bowel Cancer

Methods for establishing and maintaining epidermal suspension cultures have been applied to culturing normal human colonic mucosa and mucosa from polyps of patients with adenomatosis of the colon and rectum (ACR). *In vitro* studies on families of kindreds with ACR and its variant forms including the Gardner syndrome are being intensively conducted to define indices that represent phenotypic expressions of preneoplasia and to predict carriers of the gene defect before clinical signs appear (Danes, 1978; Danes and Gardner, 1978).

Cultured human skin fibroblasts from patients with ACR have been studied for a variety of biochemical alterations. The appearance of abnormal phenotypic expressions characteristic of transformed cells in cultured skin fibroblasts of ACR patients has been demonstrated. Clinically asymptomatic progeny of ACR individuals fall into two groups: one exhibiting the phenotypic alterations and the other more closely resembles normal control subjects (Kopelovich *et al*, 1979). The battery of phenotypic expressions may provide reliable diagnostic indices of heritable forms of colon cancer.

Clinical Research Treatment of Large Bowel Cancer

The efficacy of high dose methotrexate with calcium leucovorin rescue in the management of 27 patients with biopsy proven adenocarcinoma of the colon or rectum with advanced metastatic, objectively measurable disease has been evaluated in a randomized clinical trial. Although the therapy was well tolerated, there was no increase in the survival time of patients treated with this modality. However, a greater percentage of patients treated at ideal body weight either had a partial response or disease stabilization compared to patients who had significant weight loss. Overall five patients experienced a partial response and three patients had evidence of disease stabilization. No obvious factor in the drug dosage or severity of toxicity was found to be associated with or predictive of response (Isacoff *et al*, 1978).

To improve the postoperative prognosis of patients with Dukes' C colorectal cancer, a randomized clinical trial of adjuvant immunotherapy versus chemo-immunotherapy was initiated six years ago in 121 patients and compared to historical controls treated by surgery alone at M. D. Anderson Hospital. With the longest followup being 72 months, the data suggest that BCG alone and in combination with 5-FU prolongs the disease-free interval and the overall survival of these patients. No statistically significant difference was observed between the two treatment arms although the BCG arm appears to be slightly better (Mavligit *et al*, 1979).

A two-arm, randomized, clinical trial of adjuvant immunotherapy with immune RNA in patients with Dukes' B2 and C adenocarcinomas of the colon and rectum is being conducted. A total of 23 patients have been entered into the study, 12 having been treated with immune RNA and 11 having been entered into the control group. Increased DNCB reactivity was detected in all treated patients, and PHA and Con A blastogenic responses were increased in the majority of the treated patients. However, the observed progressive rise of immune reactivity in treated patients does not appear to be related to the disease-free interval. To date (June 1975 to the present) immunotherapy with immune RNA has not proven efficacious in the treatment of Dukes' B2 and C colorectal cancer as an adjuvant to surgery, as previously reported (Pilch *et al*, 1977). *In vitro* correlates of immunological function do not necessarily reflect *in vivo* response. Analysis of the potential therapeutic benefit of immune RNA continues.

Application of Modern Pharmacologic Methods in the Development of New Chemotherapeutic Treatments for Large Bowel Cancer

A number of model systems have been developed to evaluate and screen potential chemotherapeutic agents for eventual clinical use and to characterize the biochemical differences in responsiveness to various chemotherapeutic agents, particularly the fluoropyrimidines.

A number of murine colon tumors, varying in biological properities, have been established and used to better simulate the heterogeneity of human colon tumors. The major objective of this research project is the development of model systems which may be used for biological, biochemical, and pharmacokinetic studies to provide a better understanding of the nature and behavior of colon cancer in man and to use these systems for the detection and development of potentially useful therapeutic regimens. During the past year, six transplantable mouse colon tumor models have been used for anticancer evaluation of 284 single drug trials, 33 combination drug trials, and five surgical adjuvant drug trials. The combination of methyl CCNU and 5-FU continues to be of primary interest. However, no combination has been more than modestly potentiating (Griswold and Corbett, 1978). The inclusion of additional mouse colon tumors to the series will hopefully better reflect the heterogeneity of colorectal tumors in man and allow the selection of improved single and combination agents for trial in man.

The chemotherapeutic response of several xenografted human colorectal adenocarcinomas in immune-deficient mice and in culture has been studied. Different modalities for impairing host immunity have been assessed. New methods for the production and biological assessment of potent antithymocyte serum have been developed and used successfully in xenografting human colon carcinomas. Six lines of colorectal xenografts, each retaining their human characteristics (Houghton and Taylor, 1978) have been established in mice, and new lines are being developed and maintained in culture. The intertumor variation in response to existing chemotherapeutic agents which is observed clinically has been paralleled in the six human colorectal xenografts (Houghton and Houghton, 1978). Biochemical observations have been made on the differences and similarities that exist in fluoropyrimidine sensitive and resistant colon carcinomas. A thorough study of the metabolism of FU, 5-fluorouridine (FUR) and 5-fluoro-2'-deoxyuridine (FUdR) has been conducted. Although the xenografts are of varying degrees of differentiation, only one line ($HxELC_2$) is sensitive to inhibition by FU, and no significant differences were observed in the capability of the tumors to phosphorylate FUdR to its 5-phosphate ester (FdUMP). Tumor sensitivity therefore to FU and FUdR could not be predicted from the levels of drug uptake or analog incorporated into RNA, the inhibition of ^{3}H-UdR incorporation, or the level of FdUMP achieved (Houghton and Houghton, 1979). However, within a sensitive tumor line the fluorinated pyrimidine that produces the highest FdUMP levels induces the greatest inhibition of tumor growth.

N-Phosphonacetyl-L-aspartate (PALA) is a transition state analogue which potently and specifically inhibits aspartate transcarbamylase, the second enzyme of de novo pyrimidine nucleotide biosynthesis. PALA effectively blocks incorporation of labelled CO_2 into pyrimidine and purine nucleotide pools in human WI-38 and colon cancer HT-29 cells and inhibits their growth, but exogenous uridine stimulates the cells to grow again. Normal cells survive pyrimidine nucleotide starvation induced by PALA or induced by thymidine by entering a quiescent state in which DNA is neither synthesized nor lost (Tsuboi and Kwong, 1979).

It has been demonstrated that the chemically induced murine adenocarcinoma (MAC) tumors have similarities in common with human large bowel cancer (Double and Cooper, 1978). One line, MAC 13, has a spectrum of chemosensitivity parallel to that seen in the clinic while a second line, MAC 15, similar in histology and growth rate to MAC 13, is much less sensitive to 5-FU. Comparative biochemical studies of these two lines have been conducted by measuring a variety of enzyme activities (Cooper and Neville, 1978).

The biochemical aspects of a variety of chemotherapeutic agents have been studied using a series of transplantable murine colon tumors. An extensive survey of enzymes of pyrimidine salvage pathways in colon tumors revealed low levels of cytidine deaminase and deoxycytidylate (Brockman et al, 1978).

Cultured human colon carcinoma cells (LoVo line) have been further characterized (Drewinko et al, 1978), and the effects of thymidine deoxynucleotide (TdR) on cells treated with 5-FU have been investigated (Drewinko and Barlogie, 1978). Although TdR alone exerts a significant lethal effect on LoVo cells, it failed to prevent a lethal effect of 5-FU. However, uridine, found in the undialyzed fetal calf serum in the medium, results in a highly significant and concentration-dependent protection of the lethal effect of

5-FU. The cell killing effect of ftorafur was prevented by TdR. Treatment of LoVo cells with various concentrations of FUdR failed to elicit any significant lethal effect. The killing effect of FUR was not prevented by simultaneous incubation with TdR, but was decreased in a concentration-dependent manner by simultaneous incubation with uridine. The relative resistance of LoVo cells to 5-FU results from the limited uptake of the drug in the absence of its conversion to FUdR with subsequent inhibition of thymidine synthetase. The lethal effects elicited by 5-FU on these cells probably results from the conversion of FU to FUR followed by incorporation into various RNA species (Drewinko and Barlogie, 1978).

Application of Modern Tumor Immunobiology in Developing Diagnostic Markers, Methods of Treating, and Preventing Large Bowel Cancer

A DMH-induced tumor model in rats was used to study immunologic surveillance (Bansal S.C. *et al*, 1978a). The data suggest that a normally functioning immune system effectively suppresses the growth of some tumors. However, pretreatment with antithymocyte serum results in development of microtumors, supporting the concept that immunologic surveillance against neoplasia depends on the thymus cell system, although other possible mechanisms are not excluded. It has also been demonstrated that embryonic antigens present on colon carcinoma cells can a) elicit an immune response, b) act as tumor rejection antigens, and c) elicit a delayed type hypersensitivity reaction in a tumor host in the absence of serum-blocking factors (Bansal, B.R. *et al*, 1978). It has been shown that nonspecific immune potentiators and specific unblocking therapy can cause tumor destruction establishing the importance of serum-blocking factors *in vivo*. The role of levamisole as an immunopotentiator and unblocking serum to counteract serum-blocking factors has been substantiated (Bansal, S.C. *et al*, 1978b). The development of the methodology, supported through the National Large Bowel Cancer Project, has led to the development of an *ex vivo* method to remove IgG and its complexes (Bansal, S.C. *et al*, 1978c).

Improved procedures for isolating carcinoembryonic antigen (CEA) have been developed (Prichard and Egan, 1978). There is structural evidence to suggest that a substance similar to, if not identical with, tumor CEA, is present in normal tissues (Shively *et al*, 1978a; Prichard *et al*, 1978). The amino acid composition, amino terminal sequence, carbohydrate composition, and linkage position of the carbohydrate residues are similar in the material isolated from both tumor tissue and healthy colon lavages. In addition to the CEA present in colonic lavages of healthy individuals, the CEA-like substances present in the duodenal washings of healthy individuals and the colonic lavages of persons with ulcerative colitis were characterized (Egan and Go, 1979). Unlike CEA from normal colon washings, the CEA activity in normal epidermal washings was present in three distinct peaks.

Additional progress has been made in understanding the molecular and antigenic structure of CEA and the family of CEA-related antigens required to develop a better test for CEA. The antigenic activity of CEA appears to reside in the protein chain (Shivley and Todd, 1979). Techniques for enzymatic cleavage of CEA and separation of the resultant peptides have been developed, and sequence information has been obtained from the resultant glycopeptides (Shively and Todd, 1979). These studies have been facilitated by the development of a carbohydrate analysis requiring only small quantities of glycopeptide (Wrann and Todd, 1978). A new antigen, TEX, which cross-reacts with both CEA and normal cross-reacting antigen, (NCA), has been isolated from colonic adenocarcinomas. It is similar in structure to NCA. Both TEX and NCA possess amino terminal sequences homologous to CEA, but differ at position 21, (Kessler et al, 1978; Engvall et al, 1978). It is suggested that the backbone protein chain of this CEA molecule may be under control of a gene which shares a common evolutionary origin with those for TEX, NCA,and perhaps other cross-reactive molecules. The N-terminal aminoacid sequence of material isolated from the lavage of normal human colons is indistinguishable from CEA and homologous to it (Shively et al, 1978b).

The immunodiagnostic and immunotherapeutic importance of other human tumor-associated and organ-associated antigens, namely colon-specific antigens (CSA's) and colon-specific antigen protein (CSAp), are also being studied. CSAp has been found to be quantitatively increased in rapidly proliferating gastrointestinal tissues, especially colonic polyps and carcinomas, and it circulates in the blood of patients with colonic cancer. The immunology, immunochemistry, and immunocytochemistry of these antigens are under intense investigation. Problems associated with the isolation and purification of CSAp have been addressed, and the tissue distribution of CSAp has been verified (Pant et al, 1978). Immunocytochemical and radioimmunoassay estimations of CEA in colonic polyps and colonic adenocarcinomas have shown that CEA can vary in different specimens obtained from the same patient and can vary in content between different polyps from the same colon (Goldenberg et al, 1978a). Efforts have been directed to the area of radioimmunodetection of tumors using radiolabelled antibodies to CEA (Goldenberg, 1978). The first phase of a clinical project has demonstrated that tumors can be detected and localized by external photoscanning using this approach (Goldenberg et al, 1978b). Such an approach may be of particular relevance to immunodetection, immunodiagnosis, and immunoradiotherapy of colonic tumors.

Evidence for the induction of bowel cancer rejection by immunization against shared embryonic antigens has been obtained in immunoprevention experiments in a rat model. Similar preventive effects have been observed in females immunized to embryonic antigens as a result of multiple pregnancies (Sjogren, 1978; Nelson and Sjogren, 1978). New assays have been established for the detection of humoral antibodies to embryonic antigens shared by rat bowel carcinomas. These assays have been used in studies on sequential sera of rats developing primary bowel lesions following treatment with DMH. Antibodies to the shared embryonic antigens have been shown to appear several months before bowel carcinomas can be detected by X-ray double contrast examination or laparotomy. Evidence has also been obtained that cytotoxicity and antibody-dependent, cell-mediated cytotoxicity activity of the sequential sera are often mediated by IgM antibodies. Removal of immunoglobulins binding to protein A does not decrease these activities but sometimes results in augmentation of activity, indicating the removal of interfering factors. A new, two-phase partition technique for separating rat lymphocytes has been developed, and it has been demonstrated that lymphoid cells specifically reactive with antigens shared by rat bowel carcinomas and mid-term embryonic cells may be generated *in vitro* by cocultivation on embryo cell monolayers.

Several human colon cancer cell lines have been established and characterized biologically and morphologically. Efforts have been directed toward the isolation and identification of new colon tumor-associated antigens (Kahan *et al*, 1979), and a system has been developed for monitoring soluble antigen fractions. Growth factors for serial cell proliferation in the absence of serum have been investigated (Rutsky, 1979). *In vitro* organoid expression and CEA release kinetics have been studied in matrix profusion cultures using a perfused hollow fiber system.

A syngeneic orthotopic transplantation of MCA-38 colonic tumor cells into the submucosa of the cecum of mice has been established as a model to study the immunobiology of a primary murine colon adenocarcinoma that grows adjacent to gut-associated lymphoid tissue and metastasizes to the regional lymph nodes and to the liver. Such a model system provides a means of examining the role of the local, regional, and systemic immune responses of host resistance and metastasis as evaluated by the microleukocyte adherence inhibition assay (Goldrosen *et al*, 1978).

Emphases and Projections

The National Large Bowel Cancer Project encourages research applications concerned with causation, prevention, identification of high-risk individuals, screening/early diagnosis, pharmacological control, and treatment of colon and rectal cancer.

Model systems, now well developed, are expected to expand our concepts and knowledge concerning large bowel cancer. Such models are now being used to: (1) identify and test new anticancer drugs, (2) identify potential inhibitors of carcinogens, (3) develop approaches to immunoprevention, (4) discern factors associated with transformation of colon epithelium to precancerous lesions and carcinoma of the large bowel, and (5) assess the influence of dietary factors and the microflora in the initiation, promotion, or inhibition of large bowel cancer. These approaches may identify means to improve management of patients with this disease.

A goal of the National Large Bowel Cancer Project is to emphasize programs aimed at preventing large bowel cancer. These programs have primarily been directed toward an assessment of: (1) "high risk" populations, (2) dietary factors believed to exert an influence on large bowel carcinogenesis, (3) development of immunological approaches, and (4) examination of currently identified and new drugs which may interfere with the carcinogenic process.

Specific research projects relative to these goals include evaluating short-term assays to detect mutagens (presumptive carcinogens). The reliability and the application of such assays are being assessed in ongoing investigations.

Methods derived from research in cellular biology will be utilized to ascertain alterations in cellular behavior and to identify phenotypic expressions characteristic of high-risk individuals. Programs in screening and early diagnosis of large bowel cancer will be encouraged with particular emphasis on evaluating the factors affecting their implementation and efficacy.

The National Large Bowel Cancer Project will foster development of new chemotherapeutic drugs to treat large bowel cancer. Research will be pursued to identify targets dealing with metabolic pathways involved in nucleic acid and protein synthesis. Cell surface glycoproteins and fundamental studies of membrane structure will be continued to uncover abnormal exploitable, cellular functions.

Research proposals with novel and/or innovative therapeutic or preventive approaches will be encouraged and supported. In this regard, a Phase III, randomized, double-blind study of the antioxidant, ascorbic acid (3g/day), has been initiated at St. Mark's Hospital in London based on experimental evidence that antioxidants retard carcinogenesis. Each of the 49 patients entered has undergone colectomy and ileorectal anastomosis. The determinant of response is the number of adenomas in the rectum following surgery and therapy. In light of past experience and experimental evidence, it is hoped that this trial will hold promise for the chemoprevention of large bowel cancer, at least among patients with polyposis coli (Morson, CA23760).

Goldenberg (CA 24204), is evaluating the feasibility of using tumor-localizing antibodies to CEA for selective irradiation of CEA-producing tumors of human origin (GW-39 tumor system) with slow neutrons by combining a neutron-capturing agent (boron) with the tumor localizing antibodies.

Other Program Activities

In September 1978, the fifth workshop sponsored by the National Large Bowel Cancer Project was held, and had as its topic "Prospects for and Approaches to the Prevention of Large Bowel Cancer." This workshop included panels on epidemiology and risk factors, interaction of intestinal flora and mutagenesis, and prospects for chemoimmunoprevention of large bowel cancer.

The sixth National Large Bowel Cancer Project workshop entitled, "Approaches to Prevention and Treatment of Large Bowel Cancer" was held in January 1979. The specific subtopics included large bowel carcinogenesis and its modifiers; secondary prevention; clinical and experimental research treatment; biochemical, molecular, and pharmacologic approaches; and immunobiology.

Invitations were extended to basic scientists, clinical investigators, and physicians involved in the management of patients with colon and rectal cancer. By encouraging their collaboration and participation in these multidisciplinary programs, it is hoped that our mutual objective, i.e., the control of large bowel cancer, is fostered. A planning committee recently met to draft a program to evaluate the possible role of bile acids in large bowel carcinogenesis, the topic for the seventh National Large Bowel Cancer Project sponsored workshop to be held in January 1980.

It is believed that information gained in the exchange of current data will help in determining the goals and future direction of new and innovative research applicable to the biology and control of large bowel cancer.

A unique resource consisting of human and/or animal large bowel cell lines and cultures is being established at the American Type Culture Collection, Rockville, Maryland to foster interdisciplinary research efforts in large bowel cancer.

NATIONAL LARGE BOWEL CANCER PROJECT
(Dollars in Thousands)

Noncompeting		Competing		Total	
No.	Amount	No.	Amount	No.	Amount
35	$3,320	24	$2,472	59	$5,792

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NATIONAL PANCREATIC CANCER PROJECT

Description

The National Pancreatic Cancer Project has the aim of sponsoring basic and clinical research which promotes a better understanding of pancreatic cancer--its etiology, detection, pathology, and treatment. A committee of scientists specializing in pancreatic carcinoma continually works toward defining the research needs in each specific area, and investigator-initiated grant applications are strongly encouraged in response to these needs. Basic research is fostered in order to provide information about the natural history of the disease, and therefore studies of carcinogenesis and cell biology are warranted. Little information about the epidemiology of pancreatic carcinoma is available, so studies examining socioeconomic, environmental, and dietary factors are desirable. Early diagnosis of the disease is still a problem, although in recent years several techniques including laparoscopy, scanning, and ultrasonography have been under investigation and show some promise. Further studies of tumor markers and of immunodiagnostic tests are needed.

Now in its fifth year, the National Pancreatic Cancer Project is supporting thirty research projects. A total of forty-four research projects have been funded. A total of 164 grant applications have been reviewed in the areas of diagnosis, epidemiology, experimental biology, immunology, pathology, and treatment of pancreatic cancer.

Accomplishments

Since the last annual report was compiled, twenty articles by grantees of the Project have been accepted for publication. Thirteen are currently in print, eight appeared in 1978, and five in 1979 (see References). The remaining seven are in press.

Experimental Biology

The basic mechanism of action of selected pancreatic carcinogens has been characterized by a number of investigators. Bockman *et al.* (1979) studied the metabolism of benzo(a)pyrene crystals which were implanted for up to eight months on the surface of the pancreas in rats. The carcinogen persisted for the duration in patches predominantly comprised of multinucleated giant cells which walled off the crystals and appeared to be metabolizing them. Tumors did not develop in adjacent pancreatic tissue. The giant cells may have protected the pancreas from the potential carcinogenetic effect of benzo(a)pyrene while escaping transformation themselves.

The carcinogenicity of benzo(a)pyrene in rodents is well documented and is known to involve metabolic activation. Iqbal *et al.* (1979) examined the uptake and excretion of radioactive benzo(a)pyrene and its metabolites by the rat pancreas, with comparative studies in the liver and bile. Pinsky *et al.* (1979) studied the tissue distribution of 1-methyl-nitrosourea

(MNU) and 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) in guinea pigs. These carcinogens decompose at pH 7.4 into chemically reactive species. The methyl group of each acts as an alkylating agent, and both agents react with lysine residues in proteins, possibly contributing to the carcinogenicity of these compounds. The data indicate substantial differences in carcinogen distribution between the nucleus and whole tissue in different organs. Further studies are being carried out to examine the binding to DNA and proteins.

Pour et al. (1978) administered the carcinogen N-nitrosobis(2-oxopropyl)-amine to Syrian golden hamsters after cholecystoduodenostomy and choledochostomy to investigate a possible bile reflux mechanism as a factor in pancreatic carcinogenesis. Their findings contraindicate the importance of biliary reflux in pancreatic tumor induction.

The predominantly acinar arrangement of the exocrine pancreas has long been accepted. Bockman et al. (1978) conducted a study to determine if the dog exocrine pancreas is organized as a true acinar gland. The investigators wished to determine how the ductule-like complexes observed during induction of pancreatic tumors would develop from the acinar arrangement. Wax reconstructions prepared from portions of lobules in the dog show a branching, anastomosing system of tubules ending blindly and varying in diameter, unlike that of a true acinar gland.

The role of specific cytoplasmic receptors for reproductive steroid hormones in the process of transcription in target organs has been under investigation for some time. Rosenthal et al. (1978) examined the organ specificity of estrogen-binding proteins. Microsomal fractions of pancreas, liver, parotid gland, submaxillary gland, kidney, lung and abdominal muscles were incubated with estradiol (E_2). Over 80 percent of the E_2 was in the bound form in the supernatant of the pancreatic microsomal pellet, whereas no bound E_2 was found in the supernatants of the microsomal pellets of any of the other tissues tested.

Wu et al. (1978) studied the effects of E. coli L-asparaginase on cultured human pancreatic carcinoma. They concluded that the inhibition of growth of cultured pancreatic carcinoma cells by E. coli asparaginase is a combined function of both its L-asparaginase and L-glutaminase activity.

Diagnosis

The development of endoscopic retrograde cannulation allows for collection of pure pancreatic juice uncontaminated by bile and duodenal secretions. Rinderknecht et al. (1978) examined profiles of pure pancreatic secretions in 15 healthy human volunteers. Endoscopic retrograde cannulation of the pancreatic duct was used to collect pancreatic juice, and secretory profiles of some normal components were established. The collections of single minute samples of pure pancreatic juice reveal a more accurate profile of secretory events than does collection of pooled samples for 10 to 20 minutes as performed previously by other workers. Renner et al. (1978) studied pure pancreatic juice from two patients with acute pancreatitis. In marked contrast to the observations of the 15 normal subjects in the aforementioned study, there were high concentrations of protein throughout the period of secretin stimulation and the sporadic appearance of free proteolytic activity in many one-minute specimens throughout the collection period. These findings are consistent with the hypothesis that obstruction of ductules and intraductal activation of zymogens are important in the pathogenesis of acute pancreatitis.

Goodale *et al.* (1979) aspirated pure pancreatic fluid at the time of endoscopic retrograde cholangiopancreatography, after secretin stimulation, and analyzed for protein in patients with proven adenocarcinoma of the pancreas. It was determined that secretory abnormalities and gross tumor size and location are, to a certain extent, independent entities. Although secretion changes may precede the development of gross tumor, further work will be necessary before the actual significance for early diagnosis is known.

Recently there has been considerable interest in the development of immunodiagnostic techniques for the detection of cancer. Russo *et al.* (1978) evaluated the microleukocyte adherence inhibition (micro-LAI) assay as an immunodiagnostic test for pancreatic cancer. The micro-LAI assay specifically was able to detect pancreatic cancer and to discriminate pancreatic carcinoma from acute pancreatitis, other forms of cancer, and the normal state. This suggests an immunodiagnostic potential for the micro-LAI assay in pancreatic cancer. Harvey *et al*. (1978) identified a macromolecule containing an anticarcinoembryonic antigen-reactive substance and immunoglobulin M (IgM) in human pancreatic cancer. A method has been described for the isolation of an IgM-containing macromolecular complex from the ascitic fluid of a patient with carcinoma of the pancreas.

Pathology

In rats, azaserine is primarily a pancreatic carcinogen and only induces hepatomas with a very low incidence. Shinozuka *et al.* (1978) investigated the effects of a diet devoid of choline upon the carcinogenicity of azaserine using male Wistar rats. They concluded that such a diet changes the organ susceptibility to the carcinogenic action of azaserine, enhancing hepatocarinogenesis and reducing the action of the carcinogen on the pancreas.

Emphases and Projections

Although progress has been made toward a better understanding of pancreatic carcinoma since the establishment of the organ site program for the pancreas, much research work is still needed. Investigations on treatment, etiology (including epidemiology, cell biology, and carcinogenesis), early diagnosis (in areas of immunology, tumor markers, scanning techniques, and uptake studies), and clinical pathology are encouraged.

The National Pancreatic Cancer Project has identified treatment as a priority research area. There is great interest in studies of single chemotherapeutic agents (phase I and II trials), combinations of chemotherapeutic agents, fast neutron radiation therapy (combined with chemotherapy), and combined modality therapy.

Other Program Activities

On November 2 and 3, 1978, the third joint meeting with the American Pancreatic Association took place in Chicago. Each year, attendance at this meeting has grown, with approximately 250 investigators participating in 1978. The program has been expanded each year, and the increasing quality of the research is evident. A fourth joint meeting is planned for November 1 and 2, 1979.

Because of the importance of animal tumor models in the study of pancreatic carcinoma, a workshop in this area is being planned for late 1979. This meeting will provide an opportunity for workers to come together and exchange data.

An international workshop on cancer of the pancreas is planned for New Orleans on March 10 and 11, 1980. The format for this workshop is currently being prepared, and probably will consist of "state of the art" presentations and discussion groups. Anyone with an interest in pancreatic cancer will be welcome to attend.

A special issue of Seminars in Oncology has been edited by the Project Director and is scheduled for publication in September 1979. This issue contains eleven articles covering clinical advances in the field of pancreatic cancer including diagnosis, epidemiology, pathology, tumor markers, and treatment.

NATIONAL PANCREATIC CANCER PROJECT
(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
12	$968	14	$832	26	$1,800

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NATIONAL PROSTATIC CANCER PROJECT

Description

The National Prostatic Cancer Project has developed a research program that encompasses the areas of Etiology and Prevention, Detection and Diagnosis, and Treatment of prostatic cancer. The pursuit of targeted research through investigator-initiated efforts has resulted in application of a broad spectrum of experimental research disciplines to prostate cancer, as well as the development and evaluation of single and combination therapy modalities for local, regional, and metastatic disease.

The focal point toward which the efforts of the National Prostatic Cancer Project are directed is the prevention and improved treatment of prostatic cancer. This objective is complemented by immediate Project endeavors aimed at decreasing morbidity and increasing survival time of prostate cancer victims. Therefore, the National Project Director and the Working Cadre, with assistance of a number of ad hoc consultants, have identified priority areas of investigation which fall under the treatment category of prostatic cancer, the most significant thrust of which has been implemented through the Clinical Cooperative Trials Program.

The widespread use of endocrine therapy for prostatic carcinoma dates back to its first introduction in the early 1940's and continues in the majority of patients, to result in objective and subjective responses. However, since hormonal therapy was unable to cure metastatic disease, the desirability of studying drugs which may affect this type of cancer was recognized and led to the July 1973 initiation of the Cooperative Clinical Trials Program of the National Prostatic Cancer Project. This was the first national clinical cooperative program on chemotherapy of prostate cancer with criteria of patient randomization and clinical response tailored to the biological characteristics, metastatic behavior, and age of patients with this disease. Beginning with randomized studies of the effects of single chemotherapeutic agents on patients who fail to respond or no longer respond to conventional treatment, the program has expanded to include clinical trials using both single agents and combinations of agents aimed at patients with metastatic disease who are stable after previous treatment or who are previously untreated. Trials have also been initiated to determine the efficacy of chemotherapy as adjuvants to surgery or definitive radiotherapy in patients with earlier stages of the disease. The National Project also supports radiotherapy studies comparing extended field treatment with local field treatment. Control trials directed at determining the specific efficacy of radiotherapy are near completion. Finally, the National Prostatic Cancer Project supports efforts in the treatment category that are directed towards the synthesis of compounds with specific prostate cytotoxicity. Agents with potential activity are screened in animal, cell, and organ culture test systems, which are useful in selection of those chemotherapeutic agents for use in Phase I and II trials.

In the detection and diagnosis category, a major effort continues to be directed at developing and testing specific and sensitive immunochemical assays for prostatic acid phosphatase as diagnostic tools. Identification and development of other potentially useful biological markers including polyamines, hormone receptor profiles, the BB isoenzyme of creatine kinase, and cancer indices of various enzyme profiles in serum and prostate fluid are being tested. This work is supported by tissue and serum repositories which provide investigators ready access to cell cultures, tissue samples, and sera samples from men with normal, benign hypertrophic, and carcinomatous prostates. Additional studies are supported through the distribution, by the National Prostatic Cancer Project, of the Dunning R3327 rat tumor model of human prostatic adenocarcinoma.

The search for factors associated with prostate cancer and a better understanding of the nature and history of the disease continue. Ongoing and new projects in the Etiology and Prevention category are directed at further characterization of established animal tumor models (Dunning and Pollard rat tumors) and development of new animal models (Noble tumor). Complementing the *in vivo* model systems are *in vitro* organ and cell culture studies of human prostate tissue. The relating prostatic carcinoma specific antigens to immune mechanisms continues. To date, virologic studies of prostate cancer have shown that viral particles do not play a significant oncogenic role in human prostate cancer. Animals and *in vitro* models of prostate cancer are being studied extensively for risk factors associated with the development of the disease, and epidemiologic studies are probing the relation of genealogic, dietary, occupational, socioeconomic, sexual, and medical factors to human prostate cancer.

Accomplishments

The acid phosphatase found in the human prostate gland is antigenically unique when it is compared with acid phosphatases from other tissues and organs, (Murphy, et al., 1978). Various immunological assays for this enzyme have been developed and represent valuable tools for evaluating prostatic carcinoma at an early stage. One method is a new simple immunoassay called immunoenzyme assay (IEA). With few exceptions, results of the IEA method correspond closely with radioimmunoassays in the clinical laboratory and have the added advantage of significantly reduced costs. Also developed this year is a solid-phase fluorescent immunoassay (SPIF) for human prostatic acid phosphatase, and highly sensitive spectrophotofluorometry can quantitate as low as 3 pg of enzyme from 50 µg of serum specimen (Lee, et al., 1978). SPIF is at least 100-fold more sensitive than any existing immunoassay for prostatic acid phosphatase. The sensitivity can be increased if needed.

Preliminary clinical evaluation of SPIF is encouraging. The search for other antigen markers which are associated with or specific to cancer of the prostate has led to the first demonstration of the purification of a prostate-specific antigen which does not represent prostatic acid phosphatase. The antigen was detected in serum and was shown to be immunologically identical to the prostate tissue antigen, and is albumin-bound. Therefore, although this prostate antigen is an eutopic product of the prostate and shows no tumor specificity, it may be of potential usefulness, upon serum monitoring, in diagnosis of the prostate cancer. Another potentially important serum enzyme discovery is creatine kinase BB (Silverman, et. al., 1978). This isoenzyme is localized in the epithelium of the prostate of both benign and malignant prostate tissue and appears to be a normal secretion product which eventually becomes a constituent of prostate fluid. Thus, creatine kinase BB is in many ways similar to prostatic acid phosphatase and is of significance in relation to its presence in blood and its use as a marker for prostate cancer. Development of assay methods for prostatic steroid receptor proteins has received a great deal of emphasis (Markland, 1979; Wotiz, et al., 1979). A microassay utilizing methyltrienolone has been developed for the measurement of androgen receptor sites in the cytosol and nuclear extract of human prostatic tissue; the binding of this synthetic androgen to the progesterone-binding molecule in cytosol was eliminated by the addition of triamcinolone acetonide. When a single point assay was applied to needle biopsy specimens (200 mg of tissue), the estimated number of binding sites in nuclei averaged 83 percent of the number measured in bulk tissue (2 grams) utilizing a 7-point Scatchard analysis; the number in cytosol estimated by the microassay on needle biopsy specimens averaged 73 percent. Studies of receptor profiles have been further complemented by analyses of hormonal manipulation procedures for treatment of prostate cancer that have shown to be clearly reflected by serum testosterone and sex hormone binding globulin levels. These are readily measured and provide clinicians with the ability to monitor not only the efficacy but patient adherence to prescribed therapies. Other advances in studies of hormone binding in the prostate include the identification of prolactin binding sites in human prostate tissue utilizing immunomethodology (Witorsch, et al., 1979).

Many of the National Prostatic Cancer Project grant-supported investigations utilize Copenhagen 2331 Fischer 344 F_1 hybrid rats bearing the R3327 transplantable, hormone-responsive prostatic adenocarcinoma (Lubaroff, et. al., 1978). Because this tumor is such a useful tool in prostate cancer research, the National Prostatic Cancer Project continues to supply it to scientists throughout North America. Two new animal tumor models (Noble ~~and Pollard rat adenocarcinomas) for~~ human prostate cancer are now available for further study as a result of development and initial characterization through research efforts supported by the NPCP (Drago, et al., 1979, Chan, et al., 1978). Studies still do not indicate whether the R3327 tumor induces specific immunity in syngeneic hosts, but recent data do suggest that non-tumor antigen-specific mechanisms, which are sensitive to carrageenan, may play a role in transplantation resistance to this tumor. The availability of tissue culture lines of the R3327 tumor has also led to studies on the underlying mechanisms of tumor rejection using more relevant target cells. The R3327 adenocarcinoma is also used in investigations of substrate specificity of Δ-3 ketosteroid-5α-oxidoreductase of the rat ventra prostate (Voigt, et al., 1978). This work has demonstrated that the mode of interaction between the enzyme and substrate analogs can be modified by altering the 17β-substituent on the steroid nucleus. Utilizing this observation along with other kinetic data, steroid derivatives are currently being prepared which will have the potential of inactivating the prostatic 5α-reductase in a highly specific manner in normal rat prostate as well as in the R3327 tumor. In parallel studies, the design, synthesis, and study of novel alkylating steroids which might produce cytotoxic effects on prostatic tissue have shown that an allenic 5, 10-secosteroid carrying a pregnane side-chain inhibits 5α-reductase of rat prostate and human prostate, and causes a decrease in the wet weight of rat prostate when given *in vivo*. Analogs of this compound have been synthesized with propionate, isobutyrate, or carbomethoxy groups at C-17. The most active and least toxic of these compounds will be studied further with the R3327 tumor. Other drugs including 3-azuridine, the combination of estracyt and various platinum compounds, actinomycin, methotrexate, and some of the adenosine derivatives, such as 6N-benzyl-adenosine-monophosphate, have been tested on two animal tumor models (Pollard and R3327) of prostatic cancer originating in rats, and on organ culture of non-malignant and cancerous human prostatic tissue (Kadohama, et al., 1978). The histologic appearance, growth characteristics, 5α-reductase and arginase activities, and the metabolism of testosterone are used as indices of drug effectiveness. Of several dozen drugs already tested, five or six previously untested drugs showed definite results in the organ culture system. Since some of the drugs may require metabolic conversion to an active form, these drugs are also being tested under *in vivo* conditions with animal models.

Several cell lines of human prostate have been developed and characterized. One is a prostatic adenocarcinoma cell line (DU145) from a metastatic brain lesion that has been successfully introduced into the congenitally athymic nude mouse and is currently being serially transformed in this human tumor nude mouse model system. Three other prostate adenocarcinomas are also being serially transferred in the nude mouse, and methodology utilizing the unlabeled antibody-enzyme (PAP) technique identified the origin of the stromal elements of human tumors growing in the nude mouse. Another adenocarcinoma cell culture was isolated from a bone metastasis, and is now an established cell line (PC-3) that has undergone more than 300 population doublings. This line which has been extensively characterized, is completely aneuploid with a distinctive karyotype and more than 10 marker chromosomes. Scanning and transmission electron microscopy studies reveal that PC-3 is an epithelial cell with neoplastic characteristics. The cells clone with high efficiency, grow in soft agar, and are tumorigenic in nude, athymic mice. Application of the principles of enzyme kinetic analysis has been used to quantitate growth control of prostatic epithelial cells by peptide growth factors and glucocorticoids, and growth control of a normal prostate epithelial line, NP-2s, have also been studied (Lechner, et al., 1978).

The clinical trials program of the National Prostatic Cancer Project has completed four randomized Phase II studies of chemotherapeutic agents in patients with histologically proven advanced Stage D cancer of the prostate. These trials have demonstrated that patients who have become failures to hormonal therapy may still benefit from systemic therapy in the form of single antineoplastic agents. Therefore, current trials have been designed to examine which of these agents is most effective in this regard when used singly or in combination with other antineoplastic agents or hormonal agents. Patients with advanced disease who have become failures to hormonal therapy, patients with newly diagnosed Stage D disease, and patients with stable Stage D disease who are being treated with hormonal therapy will be entered in these trials. Based on encouraging results from earlier studies, cytoxan is being compared with methyl-CCNU and hydroxyurea in patients with advanced disease who have not had prior radiation to the pelvis. In patients who have had prior radiation to the pelvis, estracyt is being compared with vincristine and with the two in combination. The most commonly used therapeutic approach for patients with newly diagnosed Stage D disease has traditionally been either DES therapy or orchiectomy; these regimens are now being compared with DES plus cytoxan and with cytoxan plus estracyt.

In summary, over 1100 patients have been randomized to ten chemotherapy protocol studies in nine participating institutions throughout the United States. The different protocols are designed to evaluate single and combined chemotherapeutic agents in patients with histologically proven metastatic (Stage D) prostatic cancer. These protocols are further divided to consider patients who have had prior extensive radiotherapy and cannot be treated with myelosuppressive agents. Based on objective response criteria, 5-FU, streptozotocin, cytoxan, prednimustine, estracyt, and DTIC have proven effective and have increased survival time (Murphy, et al. 1979). Additional studies in progress to treat clinically stable Stage D patients and newly diagnosed Stage D patients with combinations of hormonal and chemotherapeutic agents suggest that the combination of DES and cytoxan may be acting to delay progression of disease in the newly diagnosed and stable Stage D patients. The results of the National Prostatic Cancer Project Clinical Trials Program to date have been summarized by Schmidt, J.D., et. al. (1979).

Another treatment project designed to determine the actual incidence of lymph node metastases in cancer of the prostate, their location, and their number as well as their influence on prognosis has been completed. After staging laparotomy, this project was also designed to evaluate the efficacy of local irradiation of the prostate vs prostate plus pelvis irradiation in patients without positive nodes and the efficacy of pelvic irradiation vs pelvis plus para-aortic in patients with lymph node metastases. One hundred patients were accessioned and most of the questions which could be asked concerning the risk of lymph node involvement were answered. It was evident that patients with positive lymph nodes had a high incidence of failure due to distant metastases, necessitating another approach than radiotherapy alone. In addition, the morbidity of the surgical staging procedure was high in a number of patients, necessitating a new approach to the combination of radiation and surgery in prostatic cancer.

Other Program Activities

This year the National Prostatic Cancer Project identified two topics of growing investigational activity and importance in prostate cancer. As in the past, experts were assembled to review, evaluate, and provide direction for future programmatic implementation and impact. One of these areas of concern was the need to identify hormone-sensitive and hormone-insensitive tumors and the obvious associated implications for the diagnosis and treatment of prostatic cancer. Much of the confusion that exists in this area results from a lack of standardized reliable techniques for detecting and measuring prostate hormone receptors. Thus, a workshop on the current evaluation of the status of hormone receptors and other factors as related to prostatic cancer was held at the Fred Hutchinson Cancer Research Center, Seattle, Washington, March 4-6, 1979.

The second area addressed by scientists assembled by the National Prostatic Cancer Project was in response to the growing need for appropriate models for study of human prostate cancer. On May 7 and 8, 1979, a special planning meeting was held at Roswell Park Memorial Institute in Buffalo, New York, that was devoted to an updated analysis of *in vitro* and *in vivo* model systems and their relation to the understanding and future studies of prostate cancer. Attended by over 25 contributors and participants, the data and discussions presented identified those systems which fulfill criteria of animal and cellular models.

Emphases and Projections

The National Prostatic Cancer Project will continue to investigate and implement programs and strategies for experimental and clinical research which, based on the evaluation and analysis of current knowledge and information, will offer the best opportunities for immediate and visible success at all levels of endeavor. Research in the etiology/prevention category will continue to make use of the isologously transplanted R3327 rat prostate adenocarcinoma provided to investigators by the National Prostatic Cancer Project, and the Pollard and Noble rat prostate tumor models will also be further characterized. The *in vitro* characterization of cells grown from the human prostate in monolayer, direct suspension, and organ culture will include the study of different agents that chemically transform prostatic epithelial cells, the evaluation of carcinogen effects on the prostate, and the biochemical analysis of prolactin binding in normal and neoplastic tissue. Studies of the epidemiology and etiology of prostate cancer will emphasize genetic and endocrine risk factors, with some attention continuing to focus on the possible role which viral particles play in prostate cancer.

The detection and diagnosis category of research will reflect the growing emphasis on characterization of receptor proteins for three principal classes of steroids: androgens, estrogens, and progestins. Complementing these studies will be the search for new antigen markers for the diagnosis and staging of prostate cancer. Further characterization of creatine kinase BB and the immunochemical studies of prostatic acid phosphatase is planned. Ongoing biochemical and immunological characterization of prostate cancer differentiation will be based on animal tumor models and human prostate tissue provided by the NPCP. The treatment and clinical investigations will continue to develop, screen, and test new chemotherapeutic and cytotoxic steroid agents for prostate cancer, including those which effect DNA synthesis and the 5α-oxidoreductase system. Also, development of new assays specific for not only detection and diagnosis, but for monitoring treatment responses of prostate cancer patients will continue. The studies will primarily be based on serum samples provided to investigators by the NPCP from the repository of serum from prostate cancer patients. The cooperative clinical trials section will conduct Phase II trials to determine the efficacy of single and combination treatments of hormone and antitumor agents in patients with advanced disease. Cytoxan and estracyt were selected for new studies to be used as adjuvants on a long-term prophylactic basis to be administered in a randomized fashion with the accepted definitive treatment alone consisting of lymph node dissection and prostatectomy in one trial and external radiotherapy in a second trial. Recently, two studies to evaluate the use of chemotherapy as long-term adjuvants to surgery or definitive radiotherapy were initiated in patients with earlier stages (B_2, C, or D) of prostate carcinoma. These Phase III trials are the first to use adjuvant chemotherapy against early stages of prostatic cancer.

NATIONAL PROSTATIC CANCER PROJECT

(Dollars in Thousands)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
32	$3,100	18	$1,530	50	$4,630

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CLINICAL CANCER EDUCATION PROGRAM

Description

Since 1948 the National Cancer Institute has encouraged improvements in the quality of education relative to cancer provided to physicians and dentists, the two health professions most concerned with the diagnosis and management of malignant diseases. Medical and dental schools were eligible to apply for grants to achieve a "coordination" of cancer teaching and to provide additional experiences for undergraduate students to expand their understanding of cancer in its basic and clinical aspects. In 1966, this grant program was revised to include stipends for graduate trainees in clinical oncology in appropriate specialties, and to promote educational activities relative to cancer for practicing physicians and dentists. In addition to medical and dental schools, schools of public health, cancer institutes, and major teaching hospitals affiliated with medical schools became eligible for these grants. In the interval between 1966 and 1975, grants were awarded to a total of 112 institutions, and more than 4,500 individuals received support for periods of training relative to cancer ranging from three months for undergraduate students to two or three years for graduate trainees who received instruction chiefly in medical oncology, surgical and gynecologic oncology, pediatric oncology, cancer pathology, and radiation therapy.

In 1974, following a general phase-out imposed on all training programs at the National Institutes of Health, a new program known as the Clinical Cancer Education Program was initiated to carry forward the objectives of the earlier programs, namely, to stimulate and expand multidisciplinary efforts in cancer education at the undergraduate, graduate, and continuing education levels so that physicians and dentists might deal most effectively with the clinical aspects of cancer. This new program, as did its predecessors, provides support by means of grants for selected faculty and staff, teaching equipment and supplies, consultants, and travel, but supports no trainees. However, undergraduate and graduate students may receive salaries for portions of time devoted to cancer educational experiences. A 15-member Clinical Cancer Education Committee reviews applications for these grants, visits applicant institutions, and advises on program needs and accomplishments. The major teaching activities supported by means of these grants include curricular review and analyses, development of core-curricula on cancer, cancer courses, establishment or expansion of multidisciplinary cancer teaching experiences such as conferences, seminars, clinical rotations, and electives, the development of teaching materials and aids, exposure to visiting consultants and to specialized cancer facilities, and periods of intensified education relative to cancer of varying duration. All of the activities for which support is provided must be multidisciplinary and all must be evaluated for their efficacy.

The first Clinical Cancer Education grants were awarded in 1975 to 51 institutions for a total budget of $5 million. In 1978, awards were made to 50 ongoing grantee institutions and 41 new, renewed, or supplemental grants to 90 institutions. The budget for fiscal year 1979 ($10,904,000) permitted awards to 62 ongoing and an estimated 28 new and renewed applications.

Accomplishments

Unlike research projects, the outcome of cancer education programs cannot be judged by the contributions published by grantees in scientific journals. Improvements in the scope and quality of cancer instruction, in the extent of multidisciplinary cancer teaching activities, in the numbers of undergraduate and graduate students seeking specialized periods of cancer instruction, and in the numbers of practitioners responding to educational offerings are described by all grantees in their progress reports. Ultimately, it can be assumed that these activities lead to improvements in the quality of care provided to cancer patients by students and practitioners who benefit from these experiences. Site visitors to applicant institutions have been impressed with the extent to which the goals of the earlier programs have been achieved.

The Clinical Cancer Education Committee has reviewed 42 applications during three meetings for July 1, 1979 funding, and has visited 41 institutions. Progress reports received from 50 institutions were reviewed by members of the Clinical Cancer Education Committee at their meeting on November 1-2, 1978. Forty-six reports were considered satisfactory. Further information was requested from four grantees for clarification. Progress reports on 62 current grantees will be reviewed by the Clinical Cancer Education Committee at their meeting in November 1979; the balance were reviewed as part of renewal applications.

During fiscal year 1979, consultative site visits were made to four institutions by the Executive Secretary, sometimes accompanied by a consultant or a member of the Clinical Cancer Education Committee, for the purpose of explaining to unsuccessful applicants why their applications were disapproved or received priorities too low to fund. These visits have proved to be very useful; in almost every instance, subsequent applications were approved with higher priorities, although awards could not always be made due to budget limitations.

The series of workshops on graduate education in oncology initiated in November 1976 has proven to be very successful. A follow-up meeting to the Workshop on the Training of Gastroenterologists in Oncology was held in Bethesda in January 1978; a summary of the meeting with recommendations has been forwarded to the Training and Education Committee of the American Gastroenterologic Association and to the National Cancer Institute.

In June 1978, a Workshop on Graduate Education in Medical Oncology drew together approximately 30 persons including directors of graduate training programs in medical oncology and representatives of other disciplines which participate in such programs, to seek consensus on the content, scope, and variability which these programs should have in order to be most productive. A summary of this Workshop has been prepared. Three similar workshops were subsequently held on Graduate Education in Surgical Oncology, September 5-6, 1978; Graduate Education in Pediatric Hematology-Oncology, September 26-27, 1978; and Epidemiology and Biostatistics in Clinical Cancer Education, March 28-29, 1979. Summaries of each of these workshops have been prepared.

A workshop on Physician Education in Cancer Nutrition was held on June 4-5, 1979 to examine the scope and content of physician education in diet and nutrition as they relate to all aspects of cancer, and to determine their adequacy and also the best possible methods of providing necessary education in this subject to undergraduate medical students, residents, fellows in graduate specialty training programs, and medical practitioners.

Emphases and Projections

A workscope has been designed for a contract which will be awarded this fiscal year to develop an appropriate and valid method for the evaluation of cancer education activities which are carried out at institutions receiving the Clinical Cancer Education grants. The objectives of the current grant guidelines would be redefined, a sample of the grant applications and progress reports would be reviewed, and a system of monitoring and data analysis would be designed which would enable assessment of the individual components of each program, and their variations over a period of time.

The success of the recent workshops on graduate education in the medical specialties and related educational needs indicates a need for additional programs in other disciplines. Additional workshops are planned on Graduate Education in Cancer Pathology, Graduate Education in Cancer Neurology, and Physician Education in the Psychosocial Aspects of Cancer.

Other Program Activities

Coordination is maintained with the Training Branch, National Cancer Institute, with the Division of Cancer Control and Rehabilitation, National Cancer Institute, and to a lesser extent with the Office of Cancer Communications, National Cancer Institute. Participation is maintained in the activities of the American Association for Cancer Education and the American Cancer Society. Consultants to the Program include, in addition to the members of the Clinical Cancer Education Committee, numerous clinical oncologists throughout the country who are experts in cancer education; 21 such individuals have provided services to this Program in the past year.

CLINICAL EDUCATION

(DOLLARS IN THOUSANDS)

NONCOMPETING		COMPETING		TOTAL	
NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
62	$7,226	30	$3,678	92	$10,904

RESEARCH MANPOWER BRANCH

Description

The Research Manpower Branch supports the training of scientists who will be the mainstay of the cancer research effort ten or fifteen years hence. Because no one can foresee the direction cancer research will be taking then, it is imperative that a broadly trained nucleus of investigators be maintained who can change their research interests as new leads develop and current emphases diminish. To that end, NCI supports research training in the scientific specialties composing the broad areas of cancer etiology and prevention, cancer detection and diagnosis, and cancer treatment and restorative care. The training may be in clinical or nonclinical specialties and may be in either basic or applied research. Three grant mechanisms are used to support research training, namely:

a) the Institutional Fellowship Award;
b) the Individual Fellowship Award; and
c) the Research Career Development Award.

The first two of these awards were created in 1975 by the National Research Service Act. Institutional awards are made competitively to qualified institutions to develop or enhance research training opportunities at the predoctoral and postdoctoral level. The applicant must have the staff and facilities for the proposed program. After the award is made, the institution's training program director is responsible for selecting the trainees and for administering the program. Residencies may not be supported by this program.

Individual fellowships are awarded only for postdoctoral research training in nonprofit institutions here and abroad. An applicant for a postdoctoral fellowship must establish his acceptance by a preceptor and must present a detailed description of the research project which he will undertake as part of his research training. Residencies may not be supported by this program.

Research career development awards are not governed by the National Research Service Act. The purpose of these awards is to provide very promising young investigators the opportunity to devote full time to their development as competent independent cancer investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential.

Accomplishments

During the year, 1,550 trainees and fellows and 119 research career development awardees were supported. Their distribution in the three broad research training areas was as follows:

Institutional Fellowship Awards
(training grants)

	Predoctoral	Postdoctoral
Cancer Etiology and Prevention	365	478
Cancer Detection and Diagnosis	15	61
Cancer Treatment and Restorative Care	84	233

Individual Postdoctoral Fellowships

	Postdoctoral
Cancer Etiology and Prevention	138
Cancer Detection and Diagnosis	20
Cancer Treatment and Restorative Care	66

Research Career Development Awardees

Cancer Etiology and Prevention	78
Cancer Detection and Diagnosis	17
Cancer Treatment and Restorative Care	24

The July 1978 Workshop on the Pathobiology of Cancer referred to in last year's annual report has now been evaluated. The 80 postdoctoral trainees and fellows who attended as students unanimously recommended that the program be repeated in succeeding years for other NCI trainees. Because the NCI supports almost a thousand postdoctoral research trainees, two such courses are being planned for next fiscal year.

Some of the notable research accomplishments in the past year by postdoctoral fellows, trainees, and research career development awardees include the following:

Dr. Lewis D. Yecies, an NRSA postdoctoral fellow, has elucidated a generalized role for slow reacting substance (SRS) as a mediator of inflammation. He is studying SRS synthesis and metabolism by basophils and polymorphonuclear leucocytes from patients with chronic myelogenous leukemia.

Dr. Joan C. Kaplan, a research career awardee, has developed a system of inducible SV40-transformed hamster cells which provides a sensitive biological probe for examining mammalian DNA repair systems. This has enabled her to characterize the relationship of sister chromated exchanged formation (SCE) to cellular DNA repair processes.

Dr. Daphna Sagher has defined the molecular effects of the potent carcinogen BPDE (benzopyrene 7,8 diol, 9, 10 epoxide) on MS2 RNA infectivity in an *E. coli* cell-free system, in terms of alkylation of the RNA template and synthesis of viral-coded proteins.

Emphases and Projections

Two manpower shortage areas have been identified as being especially critical. New training programs have been designed to meet these needs. They will be inaugurated in fiscal year 1980. The first of these is designed to nearly double the country's annual output of board-certified veterinary pathologists. The second is intended to recruit many more holders of the M.D. degree into epidemiology or biostatistics by establishing new programs at six to ten schools of public health or related institutions.

RESEARCH FACILITIES BRANCH

Description

The Cancer Research Facilities Program was initiated in September 1971 with a public announcement of the availability of grant funds to create additional cancer research facilities. The essence of this announcement is set forth in the following paragraph:

> In accordance with the President's call for an expanded, intensified, and coordinated cancer research program, and under authority provided by the Congress in the fiscal year 1972 appropriation act, the National Cancer Institute initiated a program of grant-supported construction of cancer research facilities. The intent of this program is to create new physical resources for cancer research through Federal participation in the cost of new construction and renovation. Support may be provided for the construction of facilities such as basic research laboratories; clinical research facilities; animal facilities; and basic associated core, administrative, laboratory, and service space. In all instances, the facilities proposed must be intended for expansion of cancer research for at least 20 years. A purpose of this program, in addition to strengthening research capabilities at existing cancer centers, is to develop new strong multidisciplinary cancer efforts in regions of the country where they do not exist. Thus, in the consideration of applications some attention will be given to geographical distribution as well as to the relation of proposed construction to existing centers of excellent cancer research.

Justification of construction funds has been, and will continue to be, in terms of new cancer research programs and in the provision of safe facilities for accomplishing biohazardous cancer research. The primary review and evaluation of applications have been essentially scientific, considering such matters as scientific merit of the proposed program(s), the technical competence of the applicant institution staff, the intellectual environment of the applicant institution, and its scientific, fiscal, and administrative capabilities. In addition, other criteria have been considered, such as the location of the applicant institution, the applicant institution's role in the National Cancer Program, the promptness with which construction can be started, space requested commensurate with projected program scope, essential minimal facilities for those institutions with an undeveloped cancer research program, net space utilization of 60 percent or more, reasonable cost per gross square foot, and acceptable design criteria.

During fiscal year 1979, 16 construction grant applications requesting $30,529,745 were received and were reviewed by site visit teams. Following the site visits, parent review committees held additional deliberations. After the final evaluation by the National Cancer Advisory Board, 14 applications were recommended for payment in a total amount of $22,223,249.

Additionally, a carryover obligation (from fiscal year 1978) on one grant totalled $1,529,921. Two administrative supplements were awarded for a total of $72,502. Thus, the NCI Construction Program faced approved funding requests of $23,830,672 after the initial evaluation of fiscal year 1979 applications.

The Construction Program's fiscal year 1979 budget was $12 million. These funds were awarded for the following projects:

- Completion of one previous (fiscal year 1978) award:
  California Institute of Technology

- New awards for Biohazard containment facilities (laboratories and animal housing):
  Michigan Cancer Foundation
  Johns Hopkins University
  University of California, San Francisco
  University of North Carolina
  Sloan-Kettering Institute for Cancer Research
  St. Jude Children's Research Hospital

- New awards for cancer clinical research facilities:
  University of California, San Diego
  Memorial Hospital for Cancer and Allied Diseases

Five additional approved applications were not funded because sufficient NCI funds were not available.

Recent Accomplishments

The Research Facilities Branch accomplished an extensive survey of all institutions receiving cancer research support to determine the current and projected needs for new improved research facilities. New facilities were needed to accommodate expanding research activities while improved facilities were needed to correct inadequate biohazard containment, meet fire safety codes, and meet DHEW standards for animal housing facilities based upon the final report (dated May 25, 1979) in which the National Cancer Advisory Board expressed serious concern about the extent of these identified facility needs and formally recommended that the Director of NCI obtain $5 million in the fiscal year 1981 budget to correct the currently known problems. The Board also recommended annual NCI funding of $20 million a year for the next five years to meet these needs.

RESEARCH ANALYSIS AND EVALUATION BRANCH

The Research Analysis and Evaluation Branch serves as a major source of scientific information on NCI-supported research projects. Members of the Branch analyze and index the scientific content of all grants awarded by DCRRC, all NCI contracts, and all NCI intramural projects, and keep track of published results supported by grants through a literature surveillance program. This information is disseminated throughout NCI--to the other divisions, Office of the Director, Office of Cancer Communications, Financial Management Branch, Program Analysis and Formulation Branch, and the International Cancer Research Data Bank; to other NIH organizations such as the Research Documentation Section and the Research Analysis and Evaluation Branch of the Division of Research Grants; to other NIH institutes; and to other Government and private organizations. Staff members also compare pending grants and contracts with existing NCI-supported projects at the same institution to assure that there is no overlap or duplicated support for a research project.

Requests for information increased dramatically during this fiscal year, mainly because of the reorganization of the Institute initiated in 1978. DCRRC program directors have been transferred to other NCI divisions, causing a decentralization of personnel and a great increase in the number of staff members responsible for the programmatic aspects of NCI grants. Requests are therefore coming not only from former DCRRC program directors but also from their new colleagues in the other divisions who must familiarize themselves in detail with grant-supported programs. In addition, because the Branch acts as a central source of information, some of the difficulties usually resulting from a decentralization of personnel have been kept at a minimum.

Computer Information System

The heart of the operation of the Research Analysis and Evaluation Branch is the Grants Elements Network-Internal Users System (GENIUS), in use since 1975. The bulk of the data base consists of scientific data for NCI grants indexed according to pertinent terms from a list of fixed terms compiled by the Branch and according to specific key words or phrases taken by the indexer from the text of the grant application. Data can be retrieved in a variety of formats in order to respond to inquiries and prepare reports.

In addition to the scientific indexing prepared by the Branch, two other types of data are available from the system. These include administrative data obtained from the Division of Research Grants' IMPAC System and Smithsonian Science Information Exchange (SSIE) abstracts supplied by the applicants.

When completely operational, the Grants Elements Network-Internal Users System will include data from five separate computer information storage files: (1) active research grants file with its companion history file of terminated grants, (2) unfunded grants, (3) active contracts, (4) intramural research projects, and (5) training programs. All scientific and administrative data on the active and history files and the intramural research file, except for the SSIE abstracts, are searchable on the computer. The unfunded grants file consists of disapproved and approved-but-not-funded grants for the past two years. This file contains only administrative data from IMPAC plus birth dates of the principal investigators. The project title, program area, and study section are the only points of access to scientific information on these projects.

The intramural research project file was added to the GENIUS system and became operational during fiscal year 1978. It is anticipated that an active contracts file will become operational by the end of this fiscal year and a training file by fiscal year 1980. The major programming efforts in early fiscal year 1979 were directed at expanding the capabilities of the existing systems and making adaptations necessitated by changes in computer hardware and software at the NIH Division of Computer Research and Technology (DCRT).

About 80 percent of the active grants, including new proposals and type 2 requests for continuing support, and 50 percent of the intramural research projects have been entered into the system. GENIUS is maintained and operated solely by the Branch, which is greatly indebted to DCRT for help in developing and implementing the system.

During fiscal year 1979, two institutes within NIH expressed interest in using aspects of the GENIUS system as a model for their own grants scientific information systems. Based on expertise acquired from developing GENIUS, the DCRT programmer assigned to this Branch is now assisting one of the institutes in this effort.

During this year, staff of the Branch also explained and demonstrated the GENIUS system in detail to representatives of Enviro Control, Inc., a contractor chosen to review and compare the science information systems within NCI and NIH in terms of their content, quality, capabilities, and usage. Within the next two years, the contractor will characterize eight information systems, examining their types of information classification, sources, operating personnel, and retrieval products, as well as user satisfaction.

Requests For Information

Requests from the Branch are made daily and vary in complexity. Most are now answered by using the GENIUS system, but other sources of information are maintained and used frequently by the Branch. These include copies of grant applications and contract proposals for active projects, progress reports, study section summary statements, reprints of published grant-supported papers, and documents concerning individual trainees and fellows. The Branch has also developed several unique files of information, including a file that lists the names and backgrounds of principal investigators on all grants submitted to NCI. During this year, the PI file was used often by Branch members as well as by NCI staff looking for and verifying the names of scientists with a particular expertise to send on site visits.

Records indicate that during calender year 1978, the number of requests increased by almost 60 percent, from 397 in 1977 to 623 in 1978. Requests from NCI's Office of the Director (OD) represent 43 percent of the total, with 30 percent of the total coming from the Office of Cancer Communications, OD. The remainder of the requests came from other NCI divisions (31.3 percent), reflecting the increase in NCI staff involved in grants administration; other NIH organizations (3.1 percent); and non-NIH organizations and individuals (22.6 percent). This great increase in requests has made it necessary for more of the Branch staff to become involved in information retrieval while still trying to increase the flow of scientific indexing for input into GENIUS.

Requests answered cover a wide range of topics, such as the following:

1. Environmental chemical pollution
2. Radiation carcinogenesis
3. Allergies and cancer
4. Vitamin C
5. "Passive" smoking
6. Dentistry and cancer
7. Nutrition and cancer
8. Epidemiology of breast cancer
9. Immunodiagnosis
10. Diagnosis with ultrasound.

The Branch staff is now assisting the Diet, Nutrition, and Cancer Program, coordinated in the Office of the Director, in carrying out its function of developing and disseminating information on the interrelationships between diet, nutrition, and the etiology of cancer and the therapy and rehabilitation of the cancer patient. Members of the Program concluded that the GENIUS system best fit their needs for implementing this information function after examining other existing NCI information systems and considering the development of their own new system. In aiding the Program, the Branch staff currently sends to Program members copies of indexed grants identified as nutrition oriented, keeps track of pertinent grants with a special code for the computer, and answers requests received by the Program for information on nutrition and cancer.

Literature Surveillance

Published results are monitored through the Branch's literature surveillance program. About 300 major medical and scientific journals are scanned to identify those papers resulting from NCI grant-supported research. These references, and additional references obtained from reprints submitted by grantees, are arranged according to DCRRC program areas and the list is issued monthly with a subject and author index as the NCI Grant-Supported Literature Index.

The Index is the most complete record available of accomplishments of the total extramural research grant program and is entered into a computer searchable system. In calendar year 1978, about 6509 articles, representing the work of 11,569 authors, appeared in the Index.

Just as two institutes at NIH are interested in developing a science information system modeled after GENIUS, a third institute has expressed interest in beginning a grant literature surveillance program modeled after the computerized system developed by the Branch.

Communications Activities

As part of an Institute-wide effort to improve communications, the Branch Chief has been participating in NCI's Working Group on Information, established by Dr. Arthur Upton, Director of NCI, to organize scientific and technical information resources; it is comprised of representatives from all the NCI divisions. Currently, members of the Group are writing a report to Dr. Upton to inform him of their activities to date and their recommendations for better intra-Institute communication.

Staff members also serve on division and institute committees that attempt to foster better communications about NCI-sponsored research in areas judged especially significant to the National Cancer Program. Two such committees are the Steering Committee of the Breast Cancer Task Force and the Office of Cancer Communications' *Ad Hoc* Group on Cancer Information Clearinghouse Operations.

The Branch maintains regular liaison with other divisions of NCI. Extra copies of grantees' reprints are sent to each division, as are copies of the SSIE abstracts for all grants. SSIE abstracts of grants concerned with specific research areas are sent on a regular basis, upon request, to NCI staff such as members of the Breast Cancer Task Force and the Laboratory of Toxicology.

This fiscal year, the Director of the Division requested that Branch staff be responsible for drafting the annual *Report of the National Cancer Advisory Board Submitted to the President of the United States for Transmittal to the Congress*. One Branch member attended meetings of the Board and contacted necessary staff members in order to draft this report, and she is now gathering information for the 1980 report.

REVIEW AND REFERRAL BRANCH

The Review and Referral Branch is responsible for (1) internal NCI program assignment of all grant applications referred to the Division of Cancer Research Resources and Centers (DCRRC); (2) assignment of grant applications for program project, core, construction, and other large instrument or special purpose grant applications to appropriate NCI review committees; (3) scientific merit review of the applications noted under (2) above; (4) review of research contract proposals submitted in response to RFP's, and (5) preparation of summary reports of the recommendations and evaluations of each committee review and of each site visit. This involves formulating goals, criteria, and strategy to meet these goals, as well as managing the activity. The latter includes analyzing, evaluating, and reporting. The Branch also serves as liaison between the Division of Cancer Research Resources and Centers and the Division of Research Grants, NIH, in matters related to review and referral.

During the period of this report, the reorganization of the National Cancer Institute resulted in a transfer of six contract peer review committees and two grant application review committees to this Branch. In addition, the workload required the use of an *ad hoc* construction application review committee. Thus, the original three committees or subcommittees have grown to 11 chartered committees and one *ad hoc* committee. As required, there were also a number of special review committees or *ad hoc* reviews developed for one-time use to assure prevention of conflict-of-interest situations; e.g., when applications were received from review committee members, or in cases when none of the chartered committees had sufficient, appropriate expertise.

The Review and Referral Branch provides initial peer review for large-scale multidisciplinary research project (program project) applications intended to generate knowledge of cancer, its biology, or control. Each application is classified for review according to its major emphasis as either a clinical or basic science proposal. The Branch also provides initial peer review of proposals for indirect support of research at Cancer Research Centers and other organizations through core funding of administrative costs and services. Such services might include computer use, biostatistics information, cell-culture maintenance and evaluation, and routine biochemistry and immunology tests. During fiscal year 1979, five committees (or subcommittees) reviewed the diverse applications submitted. During the same period six contract review committees provided peer review and technical evaluation of research support proposals submitted in response to new RFP's or as renewals of contracts previously awarded. Balance and expertise in each committee's deliberations are assured by members who are active investigators, and are nationally and internationally recognized leaders in many of the disciplines relevant to the cancer problem. The disciplinary composition of each committee is matched, insofar as possible, with the disciplinary composition of the applications it reviews. Committee recommendations regarding grants are considered by the National Cancer Advisory Board as required by the National Cancer Act.

The Grant Application Review Committees:

The Cancer Special Program Advisory Committee (CSPAC) reviews proposals requesting program project support or construction support for basic science. Review of these complex, multidisciplinary applications constitutes the bulk of the Committee's work. CSPAC has 14 members with expertise in the basic sciences related to the cause, treatment, and prevention of cancer. Members must understand medical school and university organization, administration of program projects and construction projects, and be sensitive to the effect on the applicant institution caused by initiation, continuation, or termination of a large-scale project. The group advises the NCAB and the Director, NCI, regarding the merit and probable success of the basic research program projects that come before them.

The Clinical Cancer Program Project and Cancer Center Support Review Committee was established during 1978 by merging two previously independent committees in compliance with the objective of DHEW to reduce the number of advisory committees. Through two independently functioning subcommittees, applications are reviewed for program project support concerned with clinical problems in cancer, in one case, and applications for core support of comprehensive, clinical, and specialized research centers in the other. Both subcommittees review construction applications related to their activities. Because of the complexit and volume of the work required, each of these subcommittees functions indpendently. Each subcommittee is chartered to consist of 20 members appointed by the Director of the NCI.

(A) The Cancer Center Support (Core) Review Subcommittee (CCS) provides merit review for requests to fund core grant applications submitted by designated comprehensive cancer centers and by specialized centers as well as applications to fund construction or renovation of related cancer facilities. The subcommittee is also a resource for advice on related cancer research programs, current status of ongoing centers, and identification of areas for future emphasis. Review by CCS helps alert the NCAB to the problems raised by, and the opportunities inherent in, the applications from the centers in terms of the mission of the NCI.

The responsibilities of the CCS require that the members of the Committee have broad knowledge of the basic sciences that can contribute new information about the cause and prevention of cancer and of the clinical sciences involved in prevention, diagnosis, and treatment of cancer. In addition, knowledge of the administration and organization of medical schools, universities, and free-standing cancer research organizations is essential. Sensitivity to institutions' organizational needs is important. Reviewers must be able to recognize those management practices that encourage good research.

(B) The Clinical Cancer Program Project Review Subcommittee (CCP) provides merit review of applications requesting support of clinical program projects and related cancer research programs. It also identifies areas for future emphasis, and makes suggestions for innovative approaches to the cancer problem. The review of large clinical research grant applications requires special expertise in cancer clinical trials; understanding of the special demands of research with human subjects; of hospital and medical school organization; of the administration of program projects; and, most importantly, detailed expert knowledge of the diagnosis and treatment of all types of cancer.

The Cancer Clinical Investigation Review Committee (CCI) was reassigned to the the Branch during the summer of 1978. Its major function is to review applications in support of cooperative clinical trials and related areas of cancer research. The review of cooperative clinical trials requires that the reviewers be sensitive not only to the usual issues of scientific merit of clinical research, but of the special problems involved in cooperative research where the standardization and effective management of clinical research efforts at several institutions over wide geographic distances are also important factors. The review by this committee provides the NCAB and the Director, NCI, with information concerning the problems and opportunities regarding the testing of chemotherapeutic agents and multimodality approaches to therapy.

Cancer Control Grant Review Committee (CCG). This Committee was assigned to this Branch in October 1978. Its function is to review control activity grant applications involving education in oncology, cancer epidemiology and statistics, rehabilitation research, regional programs in cancer control, and training of paramedical personnel in cancer detection techniques. The Committee advises the NCAB and the Director, NCI, on the scientific merit of these applications and identifies problems to be solved and opportunities which could be exploited.

In addition to the chartered committees, an ad hoc committee for construction was tried on an experimental basis for the final cycle of this year because (a) one committee which would have been responsible for six of the construction applications was heavily overloaded, and (b) it was thought that although construction applications should be viewed as closely allied to science, these applications are sufficiently different from other types to justify a separate review body. The experiment appears to have been successful in that no unusual problems manifested themselves during the initial review nor the NCAB review. A sufficient number of applications were involved (six) to suggest a reliable trial. Therefore, it is expected that use of a similar committee will be continued and construction applications ordinarily assigned to other committees will be assigned to it for review. This procedure is still considered exploratory and the effects of reviewing construction applications by this means will be closely monitored by review and program staff.

The contract proposals review committees, having responsibility for review of research contract proposals (as distinguished from resource contract proposals) were assigned to this Branch on approximately October 1, 1978. Previously, reviews of these proposals had been done primarily by chartered committees coordinated by program staff, many of whom served as executive secretaries on a part-time basis. Before these committees were assigned to this Branch, a number of them were consolidated from a few committees with generally similar activities into single committees (Biometry and Epidemiology, Cause and Prevention, Clinical Trials and Tumor Immunology). This consolidation of committees was done by revision of their charters in furtherance of the Department's objective to reduce the numbers of advisory bodies utilized by the Department.

Biometry and Epidemiology Contract Review Committee. This Committee advises the Director, NCI, as well as the Directors of the Division of Cancer Cause and Prevention and the Division of Cancer Research Resources and Centers on the technical merit of contract proposals responsive to RFP's relating to cancer epidemiology and biometry. Because of the nature of their studies, the intramural program staff uses such contracts to a large extent to ensure receiving sufficient data in useful forms for their research. Otherwise, the staff would not have available to it the data necessary to achieve its mission. Contracts are also used for the usual reasons by this staff. A large amount of this work is done collaboratively with extramural research institutions. During the period of this report, 44 proposals in response to one RFP were reviewed by this committee.

Cancer Control Intervention Programs Review Committee. This Committee advises the Director, NCI, and the Directors of the Division of Cancer Control and Rehabilitation and the Division of Cancer Research Resources and Centers on the technical merit of contract proposals in the fields of cancer prevention and detection, diagnosis, pretreatment evaluation, treatment, rehabilitation, and continuing care. Programs of a more applied nature than the research grant programs reviewed by the Cancer Control Grant Review Committee are stimulated and implemented through RFP's. The contract proposals received in response to such RFP's are reviewed by this Committee. Committee members must understand not only the underlying science and clinical medicine involved but the implications for cancer control of the activities which these programs support. During the period of this report this Committee reviewed 167 proposals in response to 21 RFP's.

Cause and Prevention Scientific Review Committee. This Committee advises the Director, NCI, and the Directors of the Division of Cancer Cause and Prevention and the Division of Cancer Research Resources and Centers of the technical merit of contract proposals for research into chemical, physical, and viral carcinogenesis. There are a number of programs in the Division of Cancer Cause and Prevention which use contracts in furtherance of their mission. During the period of this report, 23 proposals in response to two RFP's were evaluated by this Committee.

Clinical Trials Committee. This Committee advises the Director, NCI, as well as the Directors of the Division of Cancer Treatment and the Division of Cancer Research Resources and Centers on the scientific and technical merit of contract proposals involving clinical trials. The Division of Cancer Treatment uses such contracts when it wishes to stimulate clinical trials in which it will exercise some control of the design, conduct, and statistical analysis of the clinical trials. During the period of this report this Committee evaluated 24 proposals submitted in response to two RFP's.

Developmental Therapeutics Committee. This Committee advises the Director, NCI, as well as the Director of the Division of Cancer Treatment and the Division of Cancer Research Resources and Centers on the scientific merit of contract proposals for development of therapeutically useful anticancer agents through research in radiobiology, molecular biology, biochemistry, and pharmacology. During the period of this report this Committee reviewed three renewal proposals.

Tumor Immunology Committee. This Committee advises the Director, NCI, and the Directors of the Division of Cancer Biology and Diagnosis, the Division of Cancer Research Resources and Centers, and the Division of Cancer Treatment on the scientific merit of contract proposals involving cancer immunobiology, immunodiagnosis, immunotherapy, and the immunologic aspects of cancer cause and prevention. During the period of this report this Committee evaluated 37 renewal proposals.

Summary:

During the year, the Referral Office received and assigned approximately 3,523 applications. Of these, 78 were program projects.

The six chartered and ad hoc grants committees or subcommittees of the Branch reviewed 378 grant applications requesting a total of approximately $546,292,959. Fifty-five percent or 209 applications were recommended for approval with recommended budgets totalling approximately $210,172,235 or 38 percent of the total requested in all the approved applications. The recommended budgets amount to 23 percent of the total request for all applications reviewed. A total of $213,187,825 was disallowed in the approved grants. These data are provided in more detail in Table I. It should be noted that programmatic and financial considerations often dictate budget negotiations which further reduce the percentage paid to below the recommended level.

Table II gives details of the activities of the contracts review committees between the dates indicated. A total of 28 RFP's resulted in reviews of 278 proposals. In addition, 40 renewal proposals were reviewed. Financial data are not reported here because not all proposals recommended for approval are awarded and many of the awarded proposals are negotiated so that the financial information available to the Branch changes significantly.

The significance of the work of the Branch to the mission of the NCI is suggested by these figures. However, the true significance lies in the expert advice obtained which permits the National Cancer Advisory Board and the Director, NCI, to select for funding that research best suited to fulfill the mission of the NCI and the National Cancer Program.

TABLE 1

GRANTS REVIEW AND REFERRAL ACTIVITY: OCTOBER 1, 1978 THROUGH SEPTEMBER 30, 1979

REVIEW *GROUP	DIRECT COSTS REQUESTED: ALL APPLICATIONS: NO.	AMOUNT**	DIRECT COSTS RECOMMENDED APPROVED APPLICATIONS: NO.	AMOUNT**	DIRECT COSTS REQUESTED: APPROVED APPLICATIONS**	% AMOUNT RECOMMENDED APPROVED APPLICATIONS	AMOUNT DISALLOWED ON APPROVED APPLICATIONS**	APPROVAL RATE: NO.	AMOUNT
CAK	29	76,202255	23	34,638,064	66,641,738	52%	32,003,674	79%	45%
CCP	44	164,584,511	36	66,925,378	144,495,845	46%	77,570,467	82%	41%
CCG	139	85,911,307	28	14,978,236	29,533,066	51%	10,554,830	20%	17%
CCS	27	81,584,333	25	33,379,684	77,630,619	43%	44,250,935	93%	41%
CCI	108	72,084,273	67	19,443,626	43,162,792	45%	23,719,166	62%	27%
SRC	8	30,112,381	8	13,226,988	30,112,381	44%	16,885,393	100%	44%
AD HOC CONST.	5	12,018464	5	8,560,865	12,018,464	71%	3,457,599	100%	71%
OTHER AD HOC	18	23,795,435	17	19,019,394	23,765,155	80%	4,745,761	94%	80%
TOTAL	378	$546,292,959	209	$210,172,235	$423,360,060	50%	$213,187,825	55%	38%

Total Direct Costs recommended $210,172,235 (38% of total requested).
Total of requested budgets of disapproved applications $122,932,899 (23%).
Total of requested budgets disapproved plus amounts disallowed on approved applications $336,120,724 (62%).

	(Meeting Dates)
*CAK=CANCER SPECIAL PROGRAM ADVISORY COMMITTEE	(6/78, 10/78 and 3/79)
CCP=CLINICAL CANCER PROGRAM PROJECT REVIEW COMMITTEE	(8/78, 12/78 and 4/79)
CCC=CANCER CONTROL GRANT REVIEW COMMITTEE	(6/78, 10/78 and 3/79)
CCS=CANCER CENTER SUPPORT GRANT REVIEW SUBCOMMITTEE	(7/78, 11/78 and 3/79)
CCIRC=CANCER CLINICAL INVESTIGATION REVIEW COMMITTEE	(6/78, 11/78 and 3/79)
SRC=SPECIAL REVIEW COMMITTEE	(11/78 [2], 1,79, 2/79 [2], 3/79, 4/79 and 5/79)
AD HOC CONSTRUCTION	

**In thousands of dollars. All figures are approximate due to rounding.

TABLE II

CONTRACTS REVIEW AND REFERRAL ACTIVITY: OCT. 1, 1978 THROUGH SEPT. 30, 1979

REVIEW GROUP*	NO. OF NEW AND RENEWAL PROPOSALS	NO. OF RFP'S	MEETING DATES
CCIPRC	167	21	from 10/78 to 09/79
TIC	37**	-0-	from 12/78 to 08/79
CPSRC	23	2	from 12/78 to 09/79
DTC	3**	-0-	from 08/78 to 04/79
CTC	24	2	from 03/79 to 07/79
AD HOC	20	2	from 11/78 to 06/79
BECRC	44	1	from 09/78 to 09/79
TOTAL	318	28	

*CCIPRC=CANCER CONTROL INTERVENTION PROGRAMS CONTRACT REVIEW COMMITTEE
TIC=TUMOR IMMUNOLOGY COMMITTEE
CPSRC=CAUSE AND PREVENTION SCIENTIFIC REVIEW COMMITTEE
DTC=DEVELOPMENTAL THERAPEUTICS COMMITTEE
CTC=CLINICAL TRIALS COMMITTEE
BECRC=BIOMETRY AND EPIDEMIOLOGY CONTRACT REVIEW COMMITTEE

**RENEWALS ONLY

THE COOPERATIVE MINORITIES BIOMEDICAL PROGRAM

The Cooperative Minority Biomedical Program (CMBP), which was approved by the National Cancer Advisory Board in March 1975, represents a collaborative effort by the National Cancer Institute to implement and foster cancer research through two established minority programs--the Minority Biomedical Support Program (MBS) of the Division of Research Resources and the Minority Access to Research Careers Program (MARC) of the National Institute of General Medical Sciences. Specifically, the National Cancer Institute provides funds and programmatic advice to support meritorious research and training grants that have an impact on the overall mission of the National Cancer Program in either of these programs. The NCI also provides an administrative consultant position to each program in support of its activities.

Both the MBS and MARC program proposals are reviewed by the parent Division or Institute with the participation at all levels of NCI staff (primarily the Coordinating Executive Secretary of the CMBP) on applications with scientific research components of interest to the NCI. The DRR and NIGMS reviews are subsequently evaluated by NCI's CMBP Special Advisory Group that considers both merit and programmatic significance. The CMBP Special Advisory Group recommends NCI funding for those portions of approved applications which are judged meritorious and relevant. In fiscal year 1979, the NCI provided $890,279 to fund in whole or in part 46 applications in the MBS program. Approximately nine other NIH Institutes also contribute through collaborative agreements with DRR.

In the MARC program, four fellowships are being supported with NCI transferred funds for a total of $125,000 during fiscal year 1979.

GRANTS ADMINISTRATION BRANCH

During fiscal year 1979, the Grants Financial Section of the Grants Administration Branch (GAB) formally became a branch of its own. GAB is presently comprised of two sections in addition to the Office of the Chief, the Grants Management Section with a staff of 32 and the Processing Section with a staff of 22. GAB performs business activities attendant to administration of the NCI grant programs for research, centers, control, construction, training, and fellowships. It participates in a managerial capacity with the programs of the various NCI Divisions in the execution of extramural program plans. It interprets, applies, and participates in the formulation of policy affecting the management of grants, implements the Institute's position on extramural business management issues, provides financial and administrative analyses of grant applications and negotiates the grant awards, and processes applications and other documents related to extramural programs. This year, NCI will issue an estimated 3,430 grant awards for a total of $460,261,000.

In 1979, GAB concentrated on four major goals: equalization of grant workload; streamlining the award process; improvement of Board preparation; and improvement of resources.

Equalization of Grant Workload

GAB continued efforts begun late in fiscal year 1978 to recycle grants out of the fourth quarter. Previously 43.5 percent of grant funds were obligated in the last quarter, and fifty percent of the grants had anniversary dates in the last quarter. Late appropriations and the late release of reserves always lead to awards issued in the final month of the fiscal year, but major steps are being taken to correct the unbalanced workload caused by these factors. In fiscal year 1978, GAB shifted the start dates of 136 grants by extending and shortening funding cycles. Fiscal year 1979 saw the continuance of these activities aimed at shifting the obligation of funds and much of the grant workload out of the fourth quarter. The ultimate goal is relatively few September start dates and obligating no more than twenty-five percent of the funding in the final quarter. Competing awards issued in the final quarter will cycle in other quarters for continuation support. In addition, GAB has taken the following actions:

a. Requested early submission of noncompeting continuation applications that start in the last quarter in order to issue awards by June 30.

b. Engaged grants management specialists early in pre-award activities so that awards could be issued as soon as possible after the May Board meeting.

c. Encouraged the use of "early award" authority for grants under $35,000. The Branch also actively recommends actions to raise the ceiling to $55,000 for awards that can be made on the recommendations of initial review groups.

d. Encouraged early development of funding plans and "pay lists."

Streamlining the Award Process

The final award preparation and issuance requires three weeks. The relocation of many program staff members in different buildings, a consequence of NCI's reorganization, threatens to prolong that process. The Grants Administration Branch has been active in identifying and recommending procedural changes to reduce logistical problems. Several changes have been implemented.

a. Program directors now use their own working files rather than the official grant file to accomplish their part of the award process.

b. Signatures on pay lists rather than program directors' signatures on individual award notices provide program authority for making awards.

The Branch and the Division have also effected new efficiencies in processing approval lists (so-called "encumbrance" lists) within NCI and are recommending improved procedures for NIH. These innovations will reduce the final preparation of awards to one week.

Improving Board Preparation

The Branch has participated with the Director, DCRRC, in improving the orientation of National Cancer Advisory Board members to their duties, responsibilities, and prerogatives as they pertain to grant review. The Branch has also recommended and participated in initiating additional staff preparation for NCAB meetings. In an effort to improve and systematize the provision of summary statements to the Board, GAB has standardized the color coding and contents of the Board's bound books of summary statements and improved the index for these books. There is a continuing need to deal more effectively with the logistics of providing approximately 2,900 pages of summary statements to each Board member as advanced mailings and again at the Board meeting.

Late summary statements continue to be a problem despite the extension of time between initial review and Board review. A control system has been initiated that will provide frequently updated information concerning summary statements that have been received and those which have not. This control system allows staff a more orderly approach to preparing for Board meetings than had been possible in the past.

Improvement of Resources

To adequately administer the growing complexity of grant requirements, GAB has increased its staff, primarily in the Grants Management Section. This area has been restructured into basic, clinical, and resource support teams to conform with the general delineation of the grant programs. The Processing Section is also undergoing realignment designed to improve processing functions. The computer programs which monitor the grants process and provide continuous accurate reports are being modified to improve their usefulness as a labor-saving system and as a control for work progress. A system designed to store and produce NCI data for the Scientific Evaluation Grants (Chairmen's grants) has served as a model for the NIH system to provide consultants with income tax information.

a. Official Files: In conformance with the recently issued PHS policies on grant file documentation, the Control Sheet has been restructured to insure adequate grant file review and documentation before an award is issued. Program files have also been established which contain among other required documents the official pay lists of applications selected for funding. The filing system itself is being evaluated with the view to improving the efficiency and effectiveness of this activity.

b. Conflict of Interest: A procedure has been developed to identify institutions whose applications pose potential conflicts of interest for individual Board members. The procedure involves a computer program that identifies applications that would represent a conflict of interest if acted upon by specific Board members. This system increases staff's ability to prevent inadvertent conflict-of-interest situations.

c. NCI Grants Manual: As grant functions have increased and have been dispersed throughout the Institute, it has become apparent that formalized guidelines are needed to promote consistency and adherence to HEW/PHS/NIH grants policy. GAB has therefore increased its efforts to expand a Grants Manual started a few years ago and to modify policies and procedures on important issues.

d. WANG: The Branch has installed a word processing system (WANG) that permits joint effort by clerical staff on a single large document. The ease of editing by this mechanism has already increased both the quantity and quality of GAB's output.

Grants Management

The Grants Administration Branch is faced with the expanding complexity of requirements, more difficult access to program staff, increased participation in the review process (e.g., information summaries and attendance at site visits), and diversification and growth in both programs and program staff. It is necessary for GAB to keep pace by increasing its staff. The staff was expanded somewhat this year, but must be expanded further to be able to accomplish its functions.

GRANTS FINANCIAL AND DATA ANALYSIS BRANCH

The Grants Financial and Data Analysis Branch is responsible for fund control, for maintaining financial data, for providing information to requestors inside and out of NIH, and for analysis of financial data necessary to provide funding guideline recommendations, budget preparation, and advice for grants financial policy decisions. The reorganization of NCI and the establishment of the Grants Financial and Data Analysis Branch in fiscal year 1979 have expanded the scope and volume of these responsibilities.

Computer specialists in the branch have written computer programs which have automated work previously done manually and have assisted in special projects to help handle the increasing workload more effectively. They are responsible for creating and maintaining computer programs for the Grants Financial and Data Analysis Branch and for providing programming assistance to the Grants Administration Branch, Research Analysis and Evaluation Branch, and Review and Referral Branch.

To provide fund control for NCI grants, the GFDAB maintains an accounting data set which lists all grants selected for funding as well as all applications recommended for approval in a given fiscal year. Information necessary to identify the grant, funding codes, financial information such as award amounts, and the scientific codes used in budgeting and fund control are maintained on this data set. Computer queries sort the data in many ways to reconcile NCI's totals with the Division of Financial Management, NIH; to indicate the status of funds by mechanism, Division, and research program; and to produce reports for financial plans, variance reports, and deficiency reports for the Office of Financial Management. Through daily updating of award information, it is possible to determine the status of actual obligations at any given time. Use of computer programs makes it possible to estimate commitments not yet awarded. Both types of information are used in most financial reports.

The reorganization of NCI changed fund control and the amount and type of information maintained for each grant. In order to identify actual and potential expenditures, a division code is entered for each grant. This enables staff to sort grants by NCI program, mechanism, cancer activity and division. This information is used for funding guideline recommendations and program reviews. To further simplify data processing and promote efficiency, the development of a master file to provide a single data base for grants financial information was undertaken in fiscal year 1979. Eventually it will be possible to generate from this file data sets for fund control, historical information, and tables used in preparing special reports. Currently the master file contains expanded information about the grants and unfunded approvals included on the fiscal year data set. Its contributions this year have been to expedite the updating of award data by linking directly to the NIH Division of Financial Management system and to provide better means of checking the accuracy of data.

In the past the Grants Financial Section provided data and suggested funding options to aid in developing funding guidelines for the Division of Cancer Research Resources and Centers. The decentralization of grant programs resulting from NCI's reorganization complicated the process of making funding decisions. GFDAB's role became broader and more complex. The GFDAB devised a procedure to insure communication on grant funding decisions between Divisions and the Director, NCI, and to facilitate and expedite the process by making fiscal recommendations and by providing concise program information to each Division Director and Program Director. For each round of applications, detailed lists of recommended applications arranged in priority score order by cancer activity and with individual and cumulative costs were distributed to Division and Program Directors. A form was developed which summarized recommended applications by cancer activity and provided a space for funding plan recommendations, including priority scores cutoffs and exceptions. Division Directors' recommendations were consolidated by the GFDAB for discussion at a Division Directors funding-plan meeting. By the end of the fiscal year, many of the initial problems that delayed timely funding decisions had been confronted and solved.

Program reviews were instituted in fiscal year 1979 by the Director, NCI. In these reviews, the Director discussed the funding status of grant and contract programs with each Division Director to determine the need for transferring funds from one area to another. The GFDAB provided charts and tables showing the status of grant funds in terms of commitments and requirements.

Budget preparation continues to be a major responsibility of the GFDAB. The Branch works with the Financial Manager's Office to allocate funds by grant mechanism and to advise of reasonable budget requests for grant programs. Using current data on commitments and assumptions based on historical trends as well as knowledge about specific grants and programs, the financial analysts develop requirement and funding projections for each year in each budget submission. The detailed data showing numbers and dollars for grants by Division, mechanism, type, program, thrust, and cancer activity are entered into a budget data base.

A series of computer programs run as a package against this data base produces all the crosswalk tables now required for a budget submission. The computer programs have increased the accuracy of a budget submission and reduced the paperwork and clerical time enormously. Without them it would be a leviathan task to produce the complex set of budget tables required. The automation of the system has the additional benefit of providing time for data analysis and permitting presentation of budget data in virtually any format desired. It has become a simpler task to provide each Division with data relevant to its programs and to produce a consolidated budget for all grant programs. Modifications are made as required. Throughout the course of a fiscal year, the GFDAB answers questions from the Financial Manager's Office about the various budget submissions regarding items such as funds required to pay to certain priority scores or certain percents of requirements, how additional funds would affect funding, the effects of increased or decreased funds on future years, and the impact of various funding policies.

In addition to providing advice and answering questions about grant funds and budget, the GFDAB serves as a source of current and historical information on nonscientific aspects of cancer grants for NCI staff, the Budget Office, Program and Management Staff, the Directors, NCI, DCRRC, Congress, the National Cancer Advisory Board, and the public. Monthly lists of active grants are provided to Program Directors, the Director, DCRRC, and other NCI staff. Typical requests are for: lists of unfunded grants; summaries of applications showing requested funding, amount recommended for award, and amounts awarded in a given fiscal year; and lists or summaries of grants awarded to specific states, institutions, or principal investigators. The GFDAB responds to the cancer grants portion of the Congressional Questions for the Director, NCI, for each Congressional Budget Submission. In fiscal year 1979 the questions and format were revised to provide more useful and easily accessible information.

Historical information on each grant program is available on data sets featuring detailed lists of grants and competing applications and summary tables for each fiscal year back to 1970. These data are used for budget projections and to provide historical summaries of fiscal information. Books listing grant awards by principal investigator and by state and institution are printed and distributed to NCI staff each fiscal year.

In order to consolidate historical data on cancer grants, Grants Financial Data, a compendium of tables and charts summarizing data from 1970 to present is updated annually. Summary tables of requested, recommended, awarded, and unfunded amounts for each grant program are reprinted from individual data sets. Additional tables show grants by category such as research, manpower, and total grants. Other tables show awards by research thrust, cancer activity, NCI program, budget category, type of institution, and state and institution. For Manpower Programs tables show number of trainees and categorize trainees by academic or professional degree. Lists of awards for the current fiscal year are provided for programs with relatively small numbers of grants. Additional tables are added as appropriate each fiscal year. For example, in fiscal year 1978, tables summarizing awards by division were added. In short the Grants Financial Data provides a central source of historical data on cancer grants, and an overview of how grant dollars are spent, trends in grant applications and awards, and the current status of grant programs as indicated by numbers of applications and awards, percents funded, geographic distribution of awards, and types of research being funded.

The Grants Financial and Data Analysis Branch was involved in several major special projects in fiscal year 1979. Two projects concern possible policy changes to deal with the expectation that future budget increases, unlike inflation, will be significantly smaller than in the past. Following a discussion with the Director, NCI, a study was done showing the impact on the Traditional Program in fiscal years 1980-1984 of three funding alternatives, maintaining a constant number of grants, funding through a designated priority score, and being held to a level budget. To provide a backdrop, historical data were provided for fiscal years 1970-1978 and a projected budget was used for 1979. Tables were prepared showing the numbers of awards, annual budget increases, priorities funded, percents of grants funded, and amounts of unfunded approvals. An alternative studied in a separate project concerned the length of grant awards. A preliminary study comparing the effects of three- and five-year awards in the Traditional Program and Program Projects was undertaken by the Branch. A more comprehensive study including other programs was requested by the National Cancer Advisory Board after the first study was outlined at the May meeting.

BUDGET DISTRIBUTION

FISCAL YEAR 1979
(Thousands of Dollars)

PROGRAM	$	$	$
Research			
Traditional Program		$183,025	
Young Investigator Awards		2,750	
Conference Grants		529	
Scientific Evaluation		1,900	
Program Projects		90,869	
Organ Site Program			
Bladder	$5,039		
Large Bowel	5,792		
Prostate	4,630		
Pancreas	1,800		
Subtotal		17,261	
Creg			
DCCP	4,066		
DCT	3,732		
Subtotal		7,798	
Clinical Cooperatives		31,867	
Radiation Development		2,475	
Subtotal Research			$338,474
Resource Development			
Centers			
Cancer Center Support Grants	63,779		
Exploratory Projects	271		
Subtotal		64,050	
Clinical Education		10,904	
Careers			
RCA	160		
RCDA	4,123		
Subtotal		4,283	
National Research Service Awards			
Individual Fellowships	3,019		
Institutional Awards	17,110		
Subtotal		20,129	
Construction		12,000	
Subtotal Resource Development			111,366
Cancer Control			
Cancer Control Grants		19,500	
Centralized Cancer Patient Data System		1,820	
Subtotal Cancer Control			21,320
TOTAL			$471,160

FISCAL YEAR 1979

DISTRIBUTION OF AWARDS
(Dollars in Thousands)

	REQUESTED		RECOMMENDED		AWARDED		UNFUNDED	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
Non-Competing Continuations	2287	$281,476	2287	$281,476	2287	$281,476	0	$ 0
Competing Renewals	829	139,800	717	117,668	453	91,909	264	25,759
New	2509	214,016	1836	149,759	777	73,093	1059	76,666
Supplements	(61)	6,507	(310)	25,376	(303)	24,682	(7)	694
TOTALS	5625	$641,799	4840	$574,279	3517	$471,160	1323	$103,119

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